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Contents

NO. 1, JULY 1961

Transplantation of Tissues (*Alvarenga Prize Lecture XX*) ..... JOHN P. MERRILL 1

Tranquilizers: Experimental Proof of the Specific Effects (*Nathan Lewis Hatfield Lecture XLV*) PETER N. WITT 9

Africa Today—Health and Environmental Influences (*Arthur Parker Hitchens Lecture V*) WILLIAM A. SODEMAN 17

The History of Opium (*Kate Hurd Mead Lecture XIII*) ..... ARTHUR DICKSON WRIGHT 22

Rush and Physick: An Important Medical Friendship ..... GEORGE F. SHELDON 28

Memoirs:

Sir Robert McCarrison (1878–1960) ..... FRED B. ROGERS 39

William Stell Newcomet (1872–1960) ..... EUGENE P. PENDERGRASS 41

Maurice S. Jacobs (1897–1960) ..... SAMUEL X RADBILL 45

John Oscar Bower (1885–1960) ..... HAROLD F. ROBERTSON 48

NO. 2, OCTOBER 1961

Liver Circulation, Liver Function, and Liver Integrity (*Mary Scott Newbold Lecture LXXXI*) RALPH W. BRAUER 49

Mouse Polyoma Virus Infection (*Mary Scott Newbold Lecture LXXXII*) ..... WALLACE P. ROWE 66

The Sickness of Philoctetes (*Edward Bell Krumbhaar Prize Essay IV*) ..... JERRY D. HARRELL 71

A Student's Note Book from William Osler's Clinics in Philadelphia ..... SAMUEL X RADBILL 77

Programs and Abstracts from the Section on General Medicine 81

Memoirs:

Carl Sheldon Williams (1872–1960) ..... ALFRED COWAN 94

Karl Ernst Paschkis (1896–1961) ..... ABRAHAM CANTAROW 95

Chevalier Lawrence Jackson (1900–1961) ..... CHARLES M. NORRIS 97

Carroll Richard Mullen (1900–1961) ..... THEODORE R. FETTER 99

NO. 3, JANUARY 1962

Contributions of Biochemistry to Psychiatry (*Alvarenga Prize Lecture XXI*) ..... SEYMOUR S. KETY 101

Heritable Disorders of Connective Tissue (*James M. Anders Lecture XL*) ..... VICTOR A. MCKUSICK 112

Management of the Chronic Mentally-Ill ..... WILLIAM P. CAMP 127

Therapeutic Use of Music in a Mental Hospital ..... HENRY R. ROLLIN 130

Thomas G. Morton and Blood Transfusion: 1869–1878 ..... WILLIAM D. SHARPE 137

A Note on the Morton Dressing Carriage ..... JOHN B. BLAKE 153

Memoirs:

William Hewson (1884–1960) ..... AUSTIN T. SMITH 156

Charles Camblos Norris (1876–1961) ..... CARL BACHMAN 158

NO. 4, APRIL 1962

Annual Report of the President ..... THOMAS M. DURANT 160

The Health Sciences—A Common Bond Among All Nations (*Arthur Parker Hitchens Lecture VI*) ..... LEROY E. BURNEY 164

Better Health for Americans: The Need for Standards of Medical Care (*James M. Anders Lecture XLI*) ..... DAVID D. RUTSTEIN 169

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OCT 16 1962

Memoirs:

Perce De Long (1880–1961) ..... Alfred Cowan 179
John Hinchman Stokes (1885–1961) ..... Donald M. Pillsbury 180
James Poland Lewis (1901–1961) ..... George M. Laws 184
John Carnett Howell (1901–1961) ..... Truman G. Schnabel 185
Robert A. Matthews (1903–1961) ..... Kenneth E. Appel 187
Robert P. Glover (1913–1961) ..... J. Roderick Kitchell 191

Annual Reports

Secretary 193; Treasurer, 195; Library, 200; Mütter Museum and College Collections, 209.

Transactions of the Sections: Programs, and Abstracts from the Section on General Medicine 211
List of College Lectures, 1961 223
Officers, Committees, Sections, and Administrative Staff of the College, 1962 224
List of Fellows 227
Suggested Form of Bequest 251
Index to Volume 29 252

TRANSACTIONS & STUDIES
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Transplantation of Tissues[1]

By JOHN P. MERRILL, M.D.[2]

ANY DISCUSSION of transplantation of the kidney should begin with a brief resumé of the problems inherent in tissue transplantation in general. Interestingly enough, the beginnings of our understanding of these problems began with investigations into the transplantations of tumors, and these two fields have proceeded side by side, each contributing much to the other. The mechanisms, which in the experimental animal cause the rejection by one species of a tumor which will grow in another, have much in common with the mechanism by which normal tissue is rejected and transplanted between the same animals. Indeed the study of tumor transplantation is in reality, with but minor differences, the study of tissue immunity. The fundamental mechanisms involved in both these phenomena have been thoroughly reviewed by a number of authors (1, 2, 3) so that it is only necessary here to give a rough sketch of what is currently believed to be at the basis of the rejection of transplanted tissue. Before embarking on such a sketch, however, it might be well to define the terms with which we deal when talking about these processes. The field of tissue transplantation is changing rapidly and even the semantic aspect of it has recently been revised. In dealing with terminology we are accustomed to use the words, "autograft" and "homograft." The first term needs no elaboration. It implies the transplantation of tissue from one part of an individual to another part of that same individual. The word, "homograft" suggests the transplantation from one individual to another of the same species. Recently, however, it has been suggested by Gorer (4) that more explicit terminology be employed. In the past I, for one, have been guilty of talking of kidney "homografts" between identical twins. This, in fact, is semantically incorrect since identical twins arise from the same fertilized ovum and therefore their tissues are antigenically identical. For this reason tissue can be exchanged between them, unlike the ordinary "homograft." In the experimental animal individuals of inbred strains are so alike that they are essentially identical twins and consequently may exchange tissue without rejection. Such grafts are called isografts. Gorer has suggested that such grafts would be more correctly termed, "isogenic homografts." This term has particular pertinence for us since once the "identity" or "isogenicity" of identical twins is firmly established, one need not be concerned about

[1] Alvarenga Prize Lecture XX, College of Physicians of Philadelphia, 2 November 1960.

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an immunologic basis for failure of the grafted kidney to survive. On the other hand, between all other individuals this now appears to be the fundamental problem and Gorer has suggested that this relationship be implied not in the term homograft but in the term "allogenic homograft."

The fundamental problem involved in the failure of an allogenic graft to be accepted by the recipient may be expressed roughly by Figure 1. Antigen reaching the lymphopoietic system of the recipient is recognized as, "foreign;" that is not isogenic. In some manner antibodies are formed against it as a result of its foreign nature. In terms of transplanted tissue, these antibodies are probably contained in or on the surface of the "sensitized" lymphocyte or plasma cell. Contact between the grafted tissue and the sensitized plasma cells brings about destruction of both tissues. Recent thinking on this subject has been summarized by an excellent symposium (5). Two additional facts which are important to our thinking should be mentioned at this point. First of all, normally functioning mature lymphoid tissue is necessary for the rejection of an allogenic graft. If this tissue is impaired by disease or by congenital malformation as in Hodgkin's disease or agammaglobulinemia, the survival of the grafted tissue is much prolonged. If the normally-functioning lymphoid tissue is damaged or destroyed by x-irradiation, no mechanism exists for the production of antibodies. Therefore the graft is not rejected or is "tolerated." Since in the course of this "radiation-induced tolerance" hematopoietic tissue is also destroyed, it is necessary to graft bone marrow from the donor of the tissue so that the blood-forming elements may be restored. The second important point is that the recognition by the recipient lymphoid tissue of "allogenic" antigen is a function of the maturity as well as the competence of the lymphopoietic system. The competence of this lymphopoietic system is a function of the development of the embryo. In one species, the rat, lymphoid tissue is not mature enough to recognize and to form antibodies against

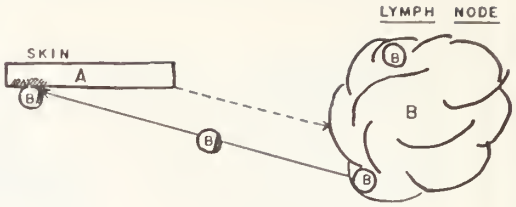

FIGURE 1

foreign tissues until two weeks after birth. In other species this function matures considerably earlier. Nevertheless it is possible to introduce into the embryo foreign antigen in the form, for example, of spleen cells at a time when its recognition system is as yet too immature to recognize the injected tissue as foreign; therefore it is tolerated. Since this tissue is tolerated, any tissue from the same donor will be tolerated subsequently following the birth and maturity of the recipient. This principle of "induced tolerance" is an extremely important one for our thinking and bears significantly upon the direction of our efforts to produce tolerance to a transplanted kidney. In the production of tolerance by the injection of mature donor tissue, however, a complication arises which again is pertinent to kidney transplantation. If by introduction of tissue into the embryo by modification of recipient lymphopoietic system by x-ray we allow the donor tissue to be tolerated, we also allow survival of tissue which in itself is immunologically competent. What this means is that the tissue introduced may be perfectly capable of multiplying and of forming antibodies against the host in which it resides. This so-called *graft-versus-host reaction* may cause serious illness or death in the recipient. Our own experience, however, suggests to us that the kidney does not contain immunologically competent cells and therefore is incapable of a *graft-versus-host reaction*. This is an important fact in the general consideration of the problem of kidney transplantation in man.

Although earlier workers did not have the benefit of the rather extensive knowledge summarized in the preceding paragraphs, it was early recognized that the transplanted kidney

like other tissues was rejected by an "immune mechanism." Exquisite surgical techniques for the anastomosis of the renal vessels were worked out by Alexis Carrel and C. S. Williamson in the 1920's. However, none of the transplanted kidneys survived although the anastomotic technique was successful. The "rejection" of these kidneys was accompanied by a characteristic infiltration with lymphocytes, whose role in the rejection process we have already discussed. Our own work in the transplantation of kidneys in dogs carried out with Dr. David Hume and Dr. Benjamin Miller resulted in much the same type of rejection. We and others were able to modify the rejection pattern of transplanted kidneys only slightly by the use of the adreno-cortico steroids. The first attempt to transplant kidney in man was made, strangely enough, by a Russian but with a notable lack of success. Our own first attempt done by Drs. Landsteiner and Hufnagle in 1945, was also unsuccessful. However, in 1950 Lawler (6) reported a case in which it seemed that success might have been achieved temporarily. This, however, did not prove to be the case. In subsequent years a number of attempts were made by French workers (7, 8) without success. Dr. David Hume and I, in 1950, began a study of a series of human cases in which kidneys taken from cadavers were anastomosed to the femoral vessels and the kidney placed in a subcutaneous pocket in the thigh. Our justification for attempting this in a human was the suggestion of some species difference in animals as well as the fact that we could enable patients to tolerate such surgery by the use of the artificial kidney. The use of a cadaver kidney and the placing of such a kidney in the thigh rather than intraperitoneally did not include the risk of a major intraabdominal procedure nor did it entail the loss of one of the patient's own kidneys no matter how poorly functioning. Nine of the seventeen cases subsequently studied were reported in 1955 (9). While none of these kidneys survived permanently, two of them functioned well enough to be of clinical benefit to the patient. One of them attained surprisingly good function for a period of almost five and one half months (Table 1). While at post mortem many of these kidneys showed the histologic changes associated with the rejection of a homograft, these were not as striking as in the experimental dog nor were they as explicit. In many cases it seemed that polymorphonuclear cells rather than lymphocytes were responsible for the destruction of the kidney and suggested perhaps that the immune mechanism in man was not as inevitable. Furthermore, the course of the two cases mentioned appeared quite different from the course followed by renal transplants in dogs. It seemed to us at that point that there might perhaps exist a species difference between man and dog which might be exploited for its clinical value; however, the case reported by Michon and Hamburger (10) which I was privileged to see in France, seemed to belie this suggestion. In the French case a previously healthy young man received a kidney transplant from his mother following the loss of his solitary kidney by trauma. This kidney functioned well almost immediately and persisted in excellent function for a period of some three weeks. At this point the kidney suddenly ceased functioning and histologically appeared much like the dog kidney with which we were so familiar. It therefore appeared to us that the prolongation of the kidney homograft in our cases might be due to the chronic uremia of the recipients and not to any fundamental

TABLE I

G. W. Case No. 9 7-14-53—Renal Function Studies for the Transplanted Kidney on the 153rd Day

Serum		Transplant urine	
BUN (mg. %)	34	C inulin (ml./min./1.73 M^2)	8.9
pH	7.4	C PAH (ml./min./1.73 M^2)	36
CO_2 (mM/L.)	20	C urea (ml./min.)	8.7
Na (mEq./L)	135	Filtration fraction	27
		Average volume (ml./min.)	2.3

difference in the immune process. We have confirmed this in noting the long survival of skin grafts in uremic patients (11). Recently we have also been able to show prolongation of the survival of skin homografts in rabbits by the administration of urea alone (12).

In 1954, however, we were stimulated to further work by a case in which Dr. Joseph Murray and I affected the successful transplantation of a kidney from a normal identical twin to his terminally ill uremic brother (13). Identity or isogenicity in this case was established by the successful transplantation of skin between them prior to the kidney graft. Since in this instance we were relatively confident that no immune mechanism would take place the transplanted kidney was placed in the right pelvic fossa of the recipient. The renal artery was anastomosed to the hypogastric artery and the renal vein to the common iliac vein. The ureter was placed directly in the bladder. This kidney functioned immediately and successfully as have eight of the nine subsequent kidney transplants we have done in identical twins. Three other such cases have been successfully done elsewhere. Two important observations resulted from this work in addition to the fact that kidneys could be successfully transplanted between identical twins. The first observation was that with the successful transplantation of a kidney malignant hypertension disappeared. We were able by observing the patients after the transplantation of a normal kidney, and again after removal of his own diseased kidney, to study the effect of these procedures upon severe renal hypertension in man. These results have been summarized elsewhere. In addition, two of the successful transplantations died at a later stage of their original renal lesion which has subsequently attacked the normal kidney graft; thus, suggesting very strongly the immune nature of glomerulonephritis in man. To avoid this in one instance, we removed both of the recipient's kidneys some ten days before transplanting the normal kidney. During this ten days this patient was entirely without renal tissue of any sort. We were able to study him very closely and to ascertain that, unlike the dog, reno-prival hypertension does not occur in man. This individual has now survived for two and one half years after the graft and has no evidence of nephritis in his transplanted kidney.

The ability to successfully transplant kidneys between identical twins gave us valuable experience in the technique of managing such patients. However the number of identical twins, one of whom is healthy and has a twin terminally ill with chronic renal failure is somewhat limited. Furthermore, these experiences did not approach the fundamental problem of renal transplantation, which is an immunologic one.

We have pointed out previously that the use of x-irradiation to destroy lymphopoietic tissue may overcome the immune response in the experimental animal. Our next approach, therefore, was the use of whole-body lethal x-irradiation. Two patients who were transferred to us from outside hospitals because of the accidental removal of a single kidney were given whole-body x-irradiation in an attempt to first successfully transplant marrow, and then a kidney. The first patient, a 31-year-old female received 600-R from a 2-MEV source. She was given pooled marrow from eleven different donors in the first 48 hours after irradiation, and on the fourth post-irradiation day a renal homograft from a non-related 4-year-old female was placed in the right thigh. Unfortunately her own marrow did not recover nor did any of the donor marrow survive as functioning tissue, and the patient subsequently died of sepsis. However, the kidney transplant at autopsy, some twenty days after the graft showed no evidence of injection suggesting that at least the immune mechanism had been avoided in this instance. The second patient was given 700-R by the same technique and received marrow cells from his mother from whom we proposed to transplant a kidney if the bone marrow graft was successful. However there was no evidence that the bone marrow survived, and we did not feel justified in removing a kidney

under these circumstances. These cases have been reported elsewhere (15). These results and those of others using lethal whole-body irradiation and bone marrow transplantation were discouraging in terms of the permanent survival of the bone marrow graft, and today we must confess that there is no evidence that a graft of bone marrow in the human has permanently survived under any conditions.

We therefore decided to try a somewhat different approach and this opportunity was afforded us in December of 1958, when we were confronted with two other twins. These individuals were apparently closely related but not identical. Their facial characteristics and hair coloring were different and the healthy twin had rejected a skin graft from his sick brother after a period of twenty-three days. This proof of immunologic competence on the part of the healthy brother against the skin antigens of his twin's proved conclusively that they were not identical. However the prolonged survival period showed that their antigenic differences were not marked although they were definite. This latter point was confirmed by the rapid rejection (5 days) of a second skin graft placed from the sick twin to the healthy brother after he had become immune to the tissue antigens of the former. Because of the chronic uremia and debilitation of the patient, the skin graft from the healthy twin on the sick recipient remained intact. These results suggested that the tissues of these two individuals were less different antigenically than those of totally unrelated individuals. If this were true, we felt that the attack necessary to prevent the immunologic system of the recipient from rejecting tissue from his brother might perhaps be necessarily less drastic. The following facts aided us in our thinking: We knew from animal experimentation that *large* doses of antigen are more effective in producing "tolerance" to a transplant than are small doses. The kidney is a large antigen. We knew also that the intravenous route is more effective for producing tolerance than the subcutaneous or other routes. Here too the analogy holds since the kidney is a vascularized antigen shedding its antigen into the venous system of the recipient. Finally, the chronically-ill uremic recipient had already shown that his disease was conducive to tolerance of his brother's tissue by his acceptance of a skin homograft from the prospective donor. We reasoned, therefore, that a smaller or sublethal dose of x-ray could be given and that the kidney might be transplanted at a time when the lymphopoietic system was temporarily incapable of responding to foreign antigen. It is in this fashion that tolerance is produced in the embryo at a time when its lymphopoietic system is too "immature" to form antibody against the injected donor antigen. A small dose of x-ray therefore might allow the recipient's bone marrow both to become tolerant and to regenerate of its own accord without the necessity for transplantation of marrow from his brother.

Following this line of thought, we then gave to the recipient 450-R of whole-body irradiation in two divided doses of 250 and 200-R seven days apart. No bone marrow was given. The white count dropped dramatically but without bone marrow transfusion made a spontaneous recovery during the course of a stormy period complicated by infection and leukopenia. The recipient's only two kidneys were removed during the nadir of his bone marrow depression. In spite of this, however, the kidney homograft functioned well and the patient was discharged from the hospital in apparent excellent health with a negative urine examination and function tests which showed normal function for a single kidney.

If the story had ended here, however, its significance might not have been so great, since it is possible that a perfect "take" might have been achieved by a purely fortuitous combination of circumstances including the rather close relationship of donor to recipient. However, six months following the operation we had evidence that we had indeed achieved true "partial tolerance". Following exposure to the sun the recipient noticed beginning rejection of the skin graft placed on his arm six months pre-

viously. At the same time he developed proteinuria and microscopic hematuria. He returned for examination and the urinary findings were confirmed. A renal biopsy showed unequivocal evidence of early rejection of the transplant. Reasoning that we might at this point be able to reinforce partial tolerance by the same techniques used to produce it, we gave him at this time a cumulative dose of 200-R whole-body x-irradiation in one month's time and daily large doses of Prednisolone. With this therapy the proteinuria markedly diminished and the hematuria disappeared. At the present time he is completely well with only a trace of protein in his urine and normal renal function (16). We believe that these results show that partial tolerance was produced for his brother's tissue and that early rejection of the kidney was aborted by the reinforcement of that tolerance by further x-irradiation and steroid therapy. Essentially this same technique has been applied by others since that time. Five months following the preliminary reports of our success with this case the group of Professor Hamburger at the Hôpital Necker in Paris utilized the identical technique to produce tolerance for a kidney transplanted between two non-identical twins. Subsequently Kuss (18) and his collaborators applied the same technique to the successful transplantation of a kidney between brother and sister, and, later, between brother-in-law and sister-in-law—the latter being the first attempt at transplantation of a kidney between totally non-related individuals, using the principles anticipated to produce partial tolerance.

Of interest is the fact that the most recent case of Hamburger and that of Kuss have both shown beginning rejection of the kidney after periods of six weeks to three months following the transplant. In both instances marked improvement in function and urinary findings has been achieved by further x-irradiation and steroid therapy. It is too early as yet to say how long the reinforcement of this partial tolerance will last, but certainly the basic principles have been validated by the cases of the French workers.

Certain lessons for the future can already be drawn from the experience with this technique gathered to date. First of all, the sick patient should be sick enough both to justify the attempt at such a procedure and to enable him to take advantage of the "tolerance" temporarily produced by uremia. Secondly, the patient and donor should be as closely related as possible, since the vast bulk of animal work suggests that the closer the antigenic make-up of the animals, the longer the survival of the homograft. It is of interest in our case, with twenty-six identical blood groups, that rejection occurred after six months. In the case of Hamburger (brother to sister) rejection began to occur at three months; while in the totally non-related patients of Kuss, rejection occurred in six weeks. Certainly such prospective donor-recipient pairs must have the same major blood groups. One of our patients who received a cadaver kidney had a major blood group incompatibility for the donor's blood. The result was thrombosis of the small vessels of the kidney due to agglutination of donor blood by patient blood when the anastomosis was established. Sex differences appear to be important in the success of tissue grafts in animals (19). This is yet to be shown in skin grafting in humans, probably because of the greater complexity of the tissue antigen structure; however, one worker has suggested that skin grafts from mother to offspring are better tolerated (20). We believe that partial tolerance for a kidney graft can be established and that this can be reinforced by subsequent x-irradiation and steroid therapy. This has yet, however, to be substantiated by animal work. The use of radiomimetic agents such as 6-Mercapto-Purine has been clearly shown to prolong skin grafts (21) and kidney homografts in dogs (22). One of our subsequent cases who received 6-Mercapto-Purine and a transplanted cadaver kidney, showed a surprising tolerance for the kidney following preparation and maintenance with this drug. Evaluation of similar agents may be productive for the future and it seems quite possible that the combined use of 6-Mercapto-Purine, nitrogen mustards, or some

other similar radiomimetic agent plus x-irradiation may be an extremely useful adjunct. Another promising approach for the future has been suggested by animal work from the Brigham group, which shows that autologus marrow removed before x-irradiation may be stored and retransfused after irradiation. In some way the immunologic capacity of the marrow is altered by freezing and storing so that it is better able to tolerate transplanted tissue when reinfused after this treatment. At the same time its ability to repopulate bone marrow is not destroyed. Similar techniques have been used for radiation protection in the treatment of tumors with high doses of x-irradiation and nitrogen mustard.

Newer knowledge of radiation dosage and techniques of delivery may also improve the anti lymphopoietic factor, and at the same time minimize the anti hematopoietic factor. Recent work in dogs has suggested that such animals given proper care (particularly with regard to prevention of infection) may tolerate higher doses of x-irradiation than have been previously thought. Certainly one increasingly important approach to the solution of the problem of renal transplantation is the care of the patient and the management of infection in the postoperative postirradiation period. Our observations in the human and the observations of Dr. Wheeler in our group give us no evidence that the kidney may react against the host, an important consideration in our thinking about the long-term results of kidney transplantation. Certainly recent results in the entire field of tissue transplantation as well as those in our own laboratory suggest that, contrary to our previous thinking, there is an organ difference and that the kidney is particularly favored in this regard. It seems further that the rejection of transplanted tissue is not an "all or none" phenomenon as had been thought previously and that "partial tolerance" may be produced. We hope that we may be able to show that this partial tolerance can not only be produced but re-enforced.

Finally it seems to me that the results with kidney transplantation have even greater significance than is suggested simply by the therapeutic achievement. The development of nephritis in transplanted kidneys of identical twins has important bearing for those interested in immunology of glomerular nephritis. The results in the study of the hypertensive patients following the total removal of two kidneys and subsequent transplantation of a poorly and then a normally functioning kidney, show in the human the course of renal hypertension in a fashion it has not been possible to do heretofor. I believe also that there is even a greater lesson in the possibility that we have produced partial tolerance for a kidney (which can be reinforced) for the kidney of a closely related but not identical donor. It seems to me possible that contact with some product of the hemolytic streptococcus or a viral agent may so change the antigenicity of one's own glomeruli that it now becomes "foreign". Under these circumstances partial tolerance for one's own kidney develops and a slow rejection of the modified glomerular antigen begins. If it is true that reinforcement of partial tolerance for a transplanted closely-related kidney can be achieved, it seems to me that such a principle might also apply to the treatment of chronic glomerulonephritis. The temporary success with the renal lesion of disseminated leukoerythrematosis and the use of 6-Mercapto-Purine is suggestive in this regard. At the present time we are treating an individual with chronic glomerulonephritis by divided doses of whole-body x-irradiation. The results while promising, are not yet conclusive. Nevertheless efforts directed along these lines I believe should prove of considerable interest and possible value to the physician concerned not only with the problems of organ and tissue replacement but also with the more general problems of the auto immune diseases.

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Tranquilizers: Experimental Proof for their Specific Effects[1]

By PETER N. WITT, M.D.[2]

I FEEL listless and tired . . . I do not care . . . I don't want to do anything, even to change the position of my body, I just want to be left in peace and lie quiet." "The next day it took a special decision to talk to somebody. If a person came to ask me something I got annoyed and tried to get away from him as soon as possible, because talking meant a special effort. And my dry mouth was not the only reason for this. There was a tendency to sit and stare into space—let things take their own course. I had to exert myself to follow a lecture. And when I attended the conference afterwards I had to make up my mind again and again about the difficult decision whether to take part in the discussion. At the same time I believed that I was able to remember things normally and understand them, but there was a reluctance to make decisions, to start something, or face any problems. This became prominent when I started to deal with my correspondence. I had three letters in front of me all dictated by a colleague. After signing the first one I mechanically put my name to the second one though I did not agree with it and knew distinctly that it would have to be rewritten. Two hours later, when the drug effect had diminished, I was terrified by what I had done and had to go through a lot of complicated procedures until I had traced and recovered the letter." "At about 5.40 p.m. I drove my car through the rush hour traffic across the city. I felt wretched, was dead tired, and was surprised that no accident happened. The driving, however, went very well. After that I had my supper in company where every action like passing a dish seemed like a momentous decision. The decision once taken, it did not need a special effort to execute it. Afterwards I was working with somebody on the translation of a paper into a foreign language. In the discussion about certain renderings I recognized a tendency in me to give in, not really caring how it would sound in the end. There was only one wish predominant, to get things over with . . . At 8.30 p.m. I went to bed and slept for 10 hours (unusually long) until I awoke in the morning. I still felt apathetic and there was a kind of veil in front of my face. I noticed that everyday actions like shaving, once they were started, were completed without any effort. The difficulty consisted in taking the decision to start anything. . ."

The foregoing are excerpts of three descriptions by persons who had taken 37.5 mg of chlorpromazine (Thorazine) for experimental purposes, this being the most thoroughly investigated and probably most widely used of the group of drugs called "tranquilizers". The authors of this paper (H. Heimann, P. N. Witt, 1955) had observed 12 healthy subjects before and after they had taken the drug. They had experienced some difficulty in summarizing the diversity of experiences and symptoms encountered in the different subjects. They tried to establish one general pattern of changes which then might be called characteristic for the drug. The listlessness, fatigue and frequently mentioned feeling as if a veil was drawn in front of the eyes reminded the participants of the effect of sedatives and sleeping drugs. A cancellation test showed that while control persons improved their performance with each repetition, people who had taken chlorpromazine did not change, staying just as slow as the first time. This could not

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be attributed to any impairment of learning because the speed of correct cancellation in the first two lines of the test increased equally for controls and drug subjects. Those that had taken chlorpromazine, however, slowed down significantly during the later part of each test while controls kept up their initial speed. It showed that endurance or the ability to keep up the speed of a performance over several minutes was impaired.

There was a distinct sequence of chlorpromazine effects apparent. Autonomous disturbances like a dry mouth, dry eyes, congestion of nose and face in the initial 30 minutes were followed by nearly 24 hours of behavioral changes like apathy, sleepiness and lack of drive. This, however, changed if you gave a different tranquilizer like reserpine (Serpasil) or meprobamate (Miltown). Did all these drugs have something special in common? Is the tranquilizer just another sleeping drug with a relatively wide margin between the sedative dose and that which produces sleep? Freyhan (1959) and several investigators with him object to the group name tranquilizers because "this classification is psychologically too seductive, pharmacologically too unspecific, and in terms of results not infrequently untrue." Klerman et al. (1960) had a similar concept in mind when they tested whether a clinically effective dose of a tranquilizer, even in a prolonged course of pharmacotherapy, could moderate anxiety and truly "sedate" without impairing significantly intellectual performances, coordination, and perception. They gained the impression that the tranquilizers meprobamate and reserpine in doses used clinically could induce a feeling of relaxation without concomitant drowsiness or psychomotor retardation. Secobarbital and phenyltoloxamine, in contrast, could not be used without producing marked drowsiness. So they came to a conclusion slightly different from Freyhan which they define as follows: "In assessing the actions of a number of psychopharmacological agents during double-blind studies on normal human subjects, observations were made bearing on the nature of sedation and tranquilization as psychophysiological states. Data were presented to indicate that sedation and tranquilization are similar states. It was concluded that the special *properties* of so-called "tranquilizer" drugs do not lie in their ability to induce a unique psychic state different from sedation, but, rather, lie in the dosage margins between their sedative effects and their effects on psychomotor performance, consciousness, and physiological functions." "The wide dosage margin between the sedative and hypnotic actions of the new drugs is also associated with different dose thresholds for effects upon psychomotor agitation and pathological mood. It appears that the different actions of the newer drugs occur at different dose thresholds. With the newer drugs, certain effects, previously occurring simultaneously, are dissociated from each other, becoming manifest at different doses." These workers seem to visualize tranquilizers as sedatives where the different stages of the drug effect are spread wider apart than in our older sleeping drugs. By adjusting the dose carefully it should be possible, according to such a view, to tranquilize with a barbiturate in a narrow low dose range or produce sleep and anesthesia with a high dose of a tranquilizer. I think we have proof now that this is not so.

I intend to bring evidence from animal experiments done in several pharmacological laboratories including our own which will answer the questions raised here. The experimental results obtained will open our eyes to the specific effects of tranquilizers in the areas where they differ from sleeping drugs. Evidence will be presented to show that they have some common properties. Our considerations do not affect the differences in side effects of the various tranquilizers which have been well documented in experimental and clinical statistics.

Let us look together at a series of behavioral experiments (Brettschneider et al., 1959): A group of 40 young Sprague-Dawley rats was handled and petted every day. They were also put regularly on a knotted rope hanging from a

pole into a transparent plastic cage. This taught them to climb up and down the rope into and out of the cage. They eventually lost their tense and fearful behavior and began to explore the cage and climb the rope. The training proper began a few weeks after these preparations. A bright light, easily visible through the plastic walls of the cage, was flashed for one second. This was followed two seconds later by an electric shock through the grid floor of the cage. The sequence was repeated once every ten minutes. While all rats tried to escape from the cage when the shock occurred, 50% of them learned very soon to avoid the shock altogether by climbing the rope after the light flashed. A little later no shocks had to be given any more. A number of individuals had changed from an unconditioned (shock) to a conditioned (light) avoidance behavior. The motivation for this behavior was fear or anxiety or both which had made them learn something. Only those rats were selected for the drug experiment which had performed satisfactorily on several days, i.e. climbed the rope not more than two seconds after the light had flashed. One, two or four mg/kg chlorpromazine was injected subcutaneously. This resulted in a suppression of the response, graded in time according to the dose given. It took the rats more and more time to climb the rope as the drug took its effect. As any response delayed more than 150 seconds was called negative, such a time interval is the upper limit of our measure or indicates complete suppression of the conditioned avoidance behavior. After 1 mg/kg suppression lasted for a few minutes, after 4 mg/kg half an hour. Rats put at this time on the ropes or on an inclined wire-mesh screen were well able to hold themselves up there. There was no indication of paralysis or diminished motor ability. They could climb but did not do it. It was not possible, however, to determine whether learning or the motivation to climb was diminished.

For comparison these same animals were injected with about equally effective doses of pentobarbital (Nembutal), namely 15 and 20 mg/kg. Such doses suppressed the rope climbing response only at a time when the animal was unable to hold itself on the rope or an inclined wire screen. To put it in descriptive terms: the sleepy and atactic rat, lying on its side, still tried to move in the direction of the rope as soon as the light flashed but did not succeed any longer in pulling itself out of the cage. The conclusion: motivation and/or learning were hardly affected by the barbiturate at a time when motor performance was severely impaired.

The question may be asked: What happens if the rat learns to leave the cage even before the light flashes? This actually occurred in a number of animals, and G. Maffii (1959) investigated the effects of tranquilizers and other agents on such a "secondary conditioned response". He gave the rats a trial every 30 minutes and termed two escapes in 15 seconds without light flash or shock a secondary conditioned response. Usually after 33 conditioning trials 90% of his rats had developed such a response and retained it. After 1.75 mg/kg chlorpromazine a 50% block of the secondary conditioned response occurred while the conditioned response was not impaired. Increasing the dose to 11.6 mg/kg resulted in 50% suppression of the conditioned response without noticeable impairment of the unconditioned response. Only after 33 mg/kg was the unconditioned response blocked and the rats did no longer try to leave the cage even after a shock.

A similar relationship of blocking first one response then the other held true for other tranquilizing agents such as promazine (Sparine), hydroxyzine (Atarax, Vistaril), azacyclonol (Frenquel), meprobamate (Equanil, Miltown) and phenaglycodol (Ultram). They have therefore been termed secondary or general deconditioning agents. For other drugs like mephenesin (Tolseram), glutethimide (Doriden) and some barbiturates the pattern was found to be different. Any dose which blocked the secondary conditioned response would affect the other two responses too. It seems that according to this nomenclature

only the tranquilizers of all the agents tested were "deconditioning agents".

It is difficult to interpret such results because the procedure of testing is complex. It is hard to define what we are testing. But even the simpler measurements of spontaneous activity in the so-called jiggle cage by Read et al. (1960) distinguishes between chlorpromazine and phenobarbital effects. For this test each mouse was kept in a cage which was mounted on a spring lever and a recorder measured the number of times the cage tipped and closed a microswitch. A control curve showed a slow decrease in spontaneous activity in the course of 80 experimental minutes. The average figure did not, however, go below 35 counts per 5 minutes. After the subcutaneous injection of 0.25, 0.5, and 1.0 mg/kg chlorpromazine activity declined immediately, the degree depending on the dose. With 0.25 mg/kg it began to recover after about 25 minutes, but not after the higher doses. In contrast, phenobarbital in the lowest dose (60 mg/kg) increased the activity during the 80 minutes experimental time. A high dose of 90 mg/kg first increased and later decreased activity. And even the highest dose of 120 mg/kg produced more than a 300% increase in counts before the mice went to sleep at the end of an hour, a distinct contrast to the behavior after chlorpromazine. The difference between the drugs was clearly not one of dosage because the stimulant effect of phenobarbital could not be produced with any dose of chlorpromazine.

The last behavioral test procedure to be discussed in this connection made use of the innate pattern of web-building behavior of spiders. Only those building two-dimensional orb-webs like Araneus diadematus Cl., the garden spider, were found suitable. The animals were kept in the laboratory in individual wooden frames 20 x 20 inches with glass sliding doors. Under favorable outside conditions they built a new web every morning after the the old one had been destroyed on the preceding afternoon. Experience has taught that drugs which affect behavior have a profound influence on the web patterns. A spider impaired in its movements by drugs like caffeine or d-amphetamine (Dexedrine) will still build a web (P. N. Witt, 1956). But such a web differs measurably from webs built on the preceding or following days. This can be proved by measuring the proportions of the webs on photographs. In order to obtain a good photographic contrast webs are made visible by spraying them with white paint. In a series of experiments each spider received 500 mg/kg pentobarbital (Nembutal) 7 hours before web-building time. All webs built the following morning were significantly different from control webs in the following proportions: 1) The catching area, represented by the area which is covered by the viscid spiral, was significantly decreased in size. 2) The webs were significantly longer than before drug application. This was calculated by dividing the horizontal diameter by the vertical diameter. 3) The angles between the radii of each web were significantly more irregular. This means that the difference between neighboring angles was increased. 4) The position of the hub in the web varied more than normal, being frequently far away from the geometric center of the nearly round catching area. 5) There was also a slightly increased number of oversized angles observed. Such angles are defined as being larger than the sum of their two neighbouring angles. All these changes had disappeared in the webs which were built one day later. In this test system chlorpromazine again caused a different kind of change. Graded according to dose, (100 mg—10 g/kg), a significant decrease in web-building frequency for one to three and more days appeared. After the highest dose only one animal built the next day and this web was slightly distorted. In all other instances if webs were built at all they were in the normal range of our control web measurements.

In order to understand such results a little better we must try to find out what makes the spider build a web. It is generally believed that hunger is the drive which determines the mood for web-building. More factors are needed to set the building process into motion

provided hunger has set the stage. There is good evidence that the early morning temperature rise after an overnight low together with the change from dark to light is involved in web-building. These two conditions are given simultaneously in the early morning hours at sun rise on a summer day. And the early morning is just the time at which all hungry spiders build their webs. Experiments carried out with spiders under constant light and temperature conditions have led to a significant decrease in web-building frequency in hungry spiders. The spiders which did not build after chlorpromazine could either not be hungry or their threshold for releasing the act of web-building had been raised in some other way. The latter seems more likely, because feeding experiments have shown that chlorpromazine spiders eat well, just as do patients under chlorpromazine treatment. This leads one to suspect that the spider has difficulties in starting its web-building comparable to those of our subject when he wanted to start his morning shave. If web-building was once begun, however, the whole subtle sequence of movements ran off practically undisturbed.

If any single one of these experiments has not convinced us that tranquilizers and barbiturates affect behavior in different ways, the parallel results of all three procedures should be regarded as strong evidence that there is a fundamental difference between the ways that the two drugs affect behavior. One, the tranquilizer, inhibits drive, possibly initiative, the ability to start something, while the other, the sleeping drug, in a sufficiently high dose, interferes with the execution of the act itself—whether this is rope-climbing, spontaneous activity, or web-building.

Attacking it from another angle and arriving at similar results qualitative rather than quantitative differences between barbiturate and tranquilizer effects were established experimentally and measurably by E. and K. Killam (1956, 1960). These investigators used unanesthetized cats which had chronically implanted electrodes in their brains. Two pairs of bipolar stimulating electrodes lay in the diffuse thalamic projection system, one in the nucleus centre median or nucleus centralis lateralis and one in the reticular formation at the level of the mesencephalon. Bipolar recording electrodes were implanted on the surface of the cat's brain. For a stabilization period of two months no drug experiments were made. Every day the animals were put into an observation chamber and watched until they went to sleep. The experimenters made sure that their animals slept by establishing criteria for sleep like: sleeping position, closed eyes, respiration regular and deep, and the characteristic synchronized sleeping EEG. Then, one of the two systems, the reticular formation or the diffuse thalamic projection system, was stimulated at one minute intervals with increasing voltage until arousal was obtained. In this way the threshold voltage for each system was determined. Arousal was defined in two ways: 1) an EEG desynchronization which outlasted stimulation, so that they knew that desynchronization was propagated and did not depend on the stimulus voltage. 2) The behavior similar to normal awakening defined by yawning, stretching, scratching, looking around "non-attentively". Such a response was assumed to be specific for arousal also because higher voltage caused a totally different behavior pattern. This can be described as "startle response".

When drugs were given, certain changes in the threshold for arousal stimulation could be measured. Reserpine 100 microgram/kg (corresponding to a human dose of about 5–10 mg/person) did not change the threshold. Chlorpromazine after 5 mg/kg (corresponding to about 250–500 mg/person) sometimes showed a slight elevation of the threshold of about 20%, and arousal was slower. Pentobarbital was chosen in a non-anesthetized or non-neurotoxic dose of 5–10 mg/kg (corresponding to 0.5–1 g/person). It elevated the arousal threshold always more than 100% and frequently more than 200%. The authors concluded from these and similar experiments that chlorpromazine and reserpine did not alter the reticular formation, where their stimulating

electrodes lay, in such a way that arousal was not possible. Pentobarbital, in contrast, causes a true depression of transmission in the reticular formation.

Keeping in mind the important role which the reticular formation plays in the waking brain (H. W. Magoun, 1958) these results lead us to have a deeper understanding of tranquilizer effects as opposed to those of barbiturates. I would like to quote verbatim some of the Killams' conclusions from these experiments because they are part of the foundations of our present-day concept of the tranquilizers' mechanism of action. "First, neither chlorpromazine nor reserpine directly alters the reticular formation so that the fundamental processes involved in the phenomenon of the "arousal" are non-functional. Second, chlorpromazine appears to augment rather than depress the neural mechanisms for the representation of the peripheral events in the reticular formation. Third, chlorpromazine also appears to enhance the inhibitory downstream effects of the reticular formation on afferent input. This alteration may be one mechanism by which chlorpromazine modifies behavior. Fourth, reserpine seems to alter some fundamental processes as yet ill-defined, controlling the organization of behavior." The authors note that, "in contrast to chlorpromazine, pentobarbital at 10 mg/kg decreased the the afferent-evoked potentials in the reticular formation . . . Conduction within the reticular formation was similarly depressed . . . The chlorpromazine induced depression in the recovery cycle of the reticular formation (established by measurements of recovery cycles in the same preparation) is qualitatively different from that induced by barbiturates."

Up to this point I have tried to bring evidence from animal experimentation to show that tranquilizers are fundamentally different from the older central depressants. This does not only relate to therapeutic range or dose, but the point of attack in the brain and the mode of action of tranquilizers can be distinguished from that of barbiturates and other sedative drugs. Let us now shift the approach and ask another question: Can animal experiments tell us also something about possible beneficial effects of tranquilizers which have not yet found application in medicine? I want to report on results of a group of recent experiments with animals using tranquilizers by S. Mallov and P. N. Witt (1961). They seem to have some bearing on human medicine. In this series barbiturates have not yet been tried so that we are unable to tell whether they would act similarly.

The experiments were performed with rats in plastic cages with a metal grid floor. Electric shocks of low AC voltage were applied at irregular intervals through the grid. No escape from the shocks was possible. In observing the animals it seemed that they built up increasing tension, anticipation and fright. Though voltage was in the course of the procedure sometimes even decreased, the animals jumped, squeaked, urinated and defecated more and more. Between shocks they sat in the corner of their cage with arched backs, hair on end and tails raised. After 0.5, 2, 4 and 7 hours the rats were sacrificed and the blood withdrawn. The free fatty acid level in the plasma was determined by the methods of Dole (1956) or Schotz et al. (1959). A difference between the shocked and control rats became soon apparent. After only 2 hours the shocked rats showed a significant rise of 32% in free fatty acids over unshocked controls. This rose after 4 and 7 hours to 51 and 126% respectively. There seems some similarity to observations on humans. Here a correlation between periods of stress, sustained drive, conflict, anxiety, anger, hostility and high serum cholesterol or high non-esterified fatty acids could be established (M. Friedman, R. H. Rosenman, 1959; J. F. Hammarsten et al., 1957; M. D. Bogdonoff et al., 1959). Such observations have formed the basis for the proposed mechanism of stress inducing through a rise in blood lipid concentrations a tendency for lipids to deposit in arterial walls. Our experiments on rats seem to be useful models because these animals have been shown to have considerably more coronary atherosclerosis after 10 months

on a high fat diet and being exposed to repeated anxiety (H. N. Uhley, M. Friedman, 1959).

In further experiments 9 rats received 4 mg/kg chlorpromazine subcutaneously 5 minutes before stressing was begun. After 4 hours these animals showed lower free fatty acid levels than those stressed without drug. They also appeared more quiet and relaxed. 8 mg/kg chlorpromazine given 5 minutes before stressing lowered free fatty acid levels even more. And if the drug was given 1 hour before stressing was begun, no increase in plasma free fatty acid levels above controls could be found. These latter animals had hardly reacted at all to the electric shocks, had shown no excessive urination and defecation, and had appeared to the observer much less tense. They were, however, not unconscious or anesthetized. They seemed to feel the shocks but react less to them.

Chlorpromazine is known to possess antiadrenergic properties in addition to its central nervous system effects. Epinephrine is a likely mediator for the increased output of free fatty acids under stress. Consequently these experiments were no basis for distinguishing between a central and an adrenergic blocking effect of the drug. In order to ascertain that the central tranquilizer effect is responsible for the prevention of a rise in the free fatty acid levels a second tranquilizer was tried. Meprobamate (Miltown) has supposedly no effect on the autonomous nervous system. When 200 mg/kg were administered as a 4% suspension in a 5% solution of gum ghatti by stomach tube one hour prior to stressing to our rats, a similar relaxation in behavior and no rise in free fatty acid levels was observed. It could also be shown that each drug administered alone to unstressed rats showed no effect on free fatty acid levels. From this it can be concluded that it is possible to inhibit the free fatty acid response of rats to stress by tranquilizers through their effect on the central nervous system. Whether similar effects on humans can be shown with therapeutic doses is an open question. But the animal experiment makes it worthwhile to spend time and effort on clinical tests.

Let us try to sum up what information these and other experiments have given us about tranquilizers. This group of drugs which comprises chlorpromazine (Thorazine), reserpine (Serpasil), meprobamate (Miltown) and several more has properties as well as an area of attack in the brain which distinguishes it qualitatively from sedatives and other centrally depressant drugs. Through their ability to diminish drive, decrease anticipatory fear and anxiety without initial excitation they may become useful in preventing physical consequences of stressful events. They have side-effects outside the central nervous system and can cause undesirable reactions which should make the physician discriminating in their use. Only when their expected beneficial effects outweigh their danger should they be prescribed. The knowledge of what tranquilizers can and cannot do, which is based on experimental evidence, will help us to pass from the period of doubt in their usefulness (which followed their enthusiastic and indiscriminate acceptance) into an era of rational therapeutic use. I am certain that there will be many patients who will profit from the specific effects of tranquilizers and who cannot be helped by any other drug.

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Africa Today—Health and Environmental Influences[1]

By WILLIAM A. SODEMAN, M.D., SC.D.[2]

DOCTOR LENTZ, Doctor Rogers, ladies and gentlemen, when your program chairman asked me to give this fifth Arthur Parker Hitchins Lecture, I felt greatly honored, not only because I was asked to address my colleagues and friends but also because I knew Colonel Arthur Parker Hitchins. My contacts with Colonel Hitchins were most casual. At one time, in the early 40's, I lunched with him when I stopped in Philadelphia on my way to the May meetings in Atlantic City. He was a gracious host and most helpful to me in my questions probing for advice on some of the vexing problems in the teaching of Preventive Medicine. I appreciated his advice and help.

When I read the title your program chairman published for my discussion today, I wondered just what I should say. I had been in Africa before but not in the area of West Africa, the scene of my recent journey. And this latter visit was one of four weeks' duration. It seems as if I am posing as an expert on problems of African health after a mere month's exposure. I reacted a bit as did my surgical chief of my interne days to some of his staff members. A number of them had returned from World War I in which they started service after having stepped one pace forward when asked to do so if interested in a particular specialty. After the war experience they had decided on that specialty for civilian practice. A month or two in a medical center gave them the final "polish" for the specialty concerned. My old chief used to say they became specialists by "going through a shower." Ladies and gentlemen, I stand before you today as the most recently showered specialist on African medical and health problems.

I visited Ghana in July 1960 to study some problems in medical education. Before entering into a survey of my experiences there I would like to tell you something of the country.

The first Europeans to visit Ghana were the Portuguese. In 1482 they established a permanent trading base. The English, along with other Europeans followed in 1553. The big attraction was gold and the trade gave the area its name—the Gold Coast. In the 17th Century the slave trade surpassed the interest in gold. Some 20 million slaves are said to have been taken from the West African coast. By 1821 the British Crown took over from the trading companies and in 1850 claimed the Gold Coast as a colony. They gained complete control from other Europeans in 1872 but it was not until 1901 that the Northern Territories were proclaimed British. Development of the area has therefore been extensive along the coast and has been less extensive as one approaches the Northern Territories. A differing people, differing language and differing climate also make for varying problems as one goes more deeply interior, conditions which affect health status and problems in disease.

In the past half century progress in education and indoctrination of Africans into colonial government established a native group capable of administrative and supervisory control. By 1949 the people were restless and anxious for self-government and finally Ghana became an independent nation on March 6, 1957. Two days later it was unanimously elected to the United Nations. Dr. Kwame Nkrumah, a prime mover in the struggle for independence became prime minister. His words at the time included the following: "My first objective is to abolish from Ghana pov-

[1] Arthur Parker Hitchins Lecture V, College of Physicians of Philadelphia, 13 December 1960.

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erty, ignorance and disease. We shall measure our progress by the improvement in the health of our people; by the number of children in school, and by the quality of their education; the availability of water and electricity in our towns and villages; and by the happiness which our people take in being able to manage their own affairs. The welfare of our people is our chief pride, and it is by this that my government will ask to be judged."

One can see the importance given health and education by the leader of this country. These six and one-half million people live in a territory about the size of Oregon, speak five major local languages aside from English, the official language. They enjoy complete freedom of religion. About two-thirds follow old African religions and are recorded as pagans in the hospital charts. About 30 per cent are Christians and the remainder are Moslems. The 1956 census estimates recorded 9920 Europeans and 2260 Syrian/Lebanese in the population.

For the medical care of Ghana's six and one-half million people there were in July 1960, 314 physicians on the registry, about one physician for every 21,000 people. And the population of the country is growing at the rate of 200,000 per year. No wonder that the Government of Ghana has decided that the country must have its own medical school. In April 1960 the Prime Minister indicated that a medical school had high priority for development and inquired if the United States Government might assist in such a venture. This request led to the establishment of an American medical team to evaluate the problem and make recommendations. This survey team, headed by myself, included Dr. Paul Cornely, Professor of Preventive Medicine, Howard University School of Medicine, skilled in hospital administration, and Robert King, a Texas architect and hospital planning consultant, experienced in designing medical facilities in tropical areas. We arrived in Ghana, June 30, 1960 to evaluate all aspects of importance in the establishment of a medical school.

The present discussion relates to the health status and problems of disease in the area. I shall say little of the medical school project except to indicate (1) that such a project is needed, (2) background education in the country is sufficiently advanced to make it feasible, (3) the national economy can support it and (4) there is no particular problem in engrafting an American medical curriculum upon a British pattern of general education. Final decisions rest above academic and educational level. Rather I want to talk about some of the general health problems of the country.

The Ministry of Health is responsible for public health services of the country. Local health agencies are still in an early stage of evolution and not developed to working level in most areas. In addition the responsibilities for the hospitals of the country rest with the Ministry. There are 45 hospitals, including special types for mental diseases, pediatrics and maternity. These represent some 3,700 beds and 1,800 cots and are both governmental and missionary in type. In addition there are four leprosaria, two for the population at large. In Accra, the capital, a city of over a quarter of a million people, there are over 1,000 hospital beds, including those of the Military Hospital, the Mental hospital and the Princess Marie Louise Hospital for children. Laboratory services are supplied by the Medical Research Institute located physically next to Korle Bu, the largest general hospital in Accra. It was at the Institute where Noguchi worked on yellow fever and died of that disease in 1928. The Institute controls the laboratories throughout the country and trains the laboratory technicians for the entire republic.

Health facilities are rather incomplete for the country as a whole. The southern area along the coast is the most highly developed. The entire country is divided into health districts and governmental and missionary hospitals are scattered throughout. Plans are well under way to establish additional health facilities. There are now 21 new health centers and 19 others either under construction or about to be started. Such centers are designed for rural areas and are of a fixed pattern, with quarters for two nurses (one a community health nurse),

two midwives, one health inspector, and several supporting employees. These health centers have clinic areas, rooms for emergencies and a maternity division including eight ward beds and a laboratory. It may be seen that, although called health centers, these units, as frequently occurs in substandard areas, are established primarily for patient care. The development of preventive health programs under a public health physician remains for the future.

One of Ghana's most important public health problems is environmental sanitation. Even in the most highly developed area, Accra, conditions are very poor. The older section of the city has a population density up to 800 or more per acre. Housing is grossly inadequate and the problem is compounded by the custom of undivided families in which the entire family group lives in one unit. As many as five people will occupy one room. Central sewage disposal does not exist. In the more pretentious housing septic tanks are used. Otherwise ordinary latrines and bucket disposal maintains. Markets are of the open primitive type with cooked foods spread out in the open. Flies are in abundance. In Accra and Kumasi, the water supply is satisfactory but in the densely populated areas is available only from open outside taps. Again in more modern housing it is piped inside as in our country and is potable.

The circumstances already described—physicians in short supply, poor environmental sanitation, shortage of public health facilities—coupled with a tropical climate give one the background for an understanding of the types of disease seen and for the major causes of mortality and morbidity. Statistics are incomplete and sketchy. They are available from registration areas which include only about 12 per cent of the population and from hospital records.

Infant mortality is high. In 1956 the infant mortality rate declined to 98, the first break below 100. In the United States in 1956 the figure was 26. The present figures in Ghana approach those of the United States for 1915 when data were first gathered on infant mortality in the United States and the rate was 99.9 per 1000. For comparison the current rate (1958) for the United States is 27.1 and is provisionally estimated at 26.4 for 1959 and 25.9 for the first one-half of 1960. In 1958 the range among states in the United States varied from 21.3 per 1000 for Rhode Island to 41.0 for Mississippi. The 1958 rates for some other countries were 15.8 for Sweden, 23.3 for the United Kingdom and 20.5 for Australia. The latest reported rate for Russia (1957) is 40.6 deaths under one year per 1000 live births. In Ghana problems of childbirth are in the hands of midwives except for complicated obstetrics. Patterned on the British system, midwives attend births within the hospitals as well as outside. Midwives require two to two and one-half years of training beyond the usual courses in nursing.

In the list of the leading causes of death problems of childbirth and the puerperium are exceeded only by malaria. As in many tropical areas, malaria is still the captain of the causes of death and the number one health problem despite the fact that malaria eradication programs are under way, some in cooperation with W.H.O. The traditional approach of residual sprays and administration of antimalarial drugs is being used in the Volta region, while in the Northern Region the entire population is being treated by incorporation of the antimalarial drug in salt in a fashion similar to that used for iodination of a population.

Acute malaria is, of course, an important disease of children and, along with malnutrition, leads the causes of admissions to the children's services in the hospitals of Accra. In visiting the wards of the hospitals, I saw striking examples of the clinical expressions of this disease, including cerebral malaria with hemiplegia in an infant of eight months.

Government hospital reports show other leading causes of mortality to be intestinal obstruction and hernia, the bronchopneumonias and tetanus. Interestingly enough in third place are motor vehicle accidents. Much of the transportation between the towns takes place on a system of macadam-type roads of good

quality. The chief means of transportation are so-called mammy wagons—trucks made into buses by plank seats as in many tropical countries. These vehicles are overcrowded by the native population carrying many of their wares. Needless to say an accident involving two of these vehicles produces a multiplicity of injuries.

Malaria also leads the list of important causes of morbidity, followed by trauma and the complications related to childbirth. Of the communicable diseases, tuberculosis, always a leader in the tropics, is second only to malaria. In 1956, over 3,000 cases were treated. A Tuberculosis Research Unit operating as a branch of W.A.C.M.R. has done extensive tuberculin surveys showing that 80 per cent of young adults are Mantoux positive by the age of 20. The other important acid fast organism, M. leprae, is also a serious problem. In 1956, for example, some 30,000 patients were treated for leprosy on an ambulatory basis. There are two leprosaria available for the care of the general public.

Of the viral infections, smallpox is still important. Despite vigorous vaccination campaigns, in 1956 extending to over one million people, 259 active cases were reported that year. Yellow fever, the other dreaded viral disease is under control. There are four centers for vaccination. As I have already stated, it was in Accra where Noguchi died in 1928 when studying the cause of yellow fever. Many believe that yellow fever originated in Africa and was introduced into the Americas by the slave trade from West Africa.

Dysenteries of bacillary, amebic and other types are important infectious diseases in Ghana. Hookworm is widespread and ascariasis even more so than hookworm. Yaws is another major problem; almost 30,000 instances being treated in the hospitals in 1956. In 1959 field units examined almost two million people for yaws. Onchocerciasis, African sleeping sickness, and schistosomiasis are of great importance and field units are operated for Simulium, tsetse, and snail control respectively.

Of the diseases more familiar to us in the United States, motor vehicle accidents have already been mentioned. Nutritional deficiencies are of great importance, especially in children. Long periods of breast feeding, up to two years, with little supplementary feeding, especially of milk or other protein containing products, make malnutrition, along with malaria, the leading condition on the wards of the pediatric units. Kwashiorkor and nutritional anemia are frequent clinical pictures, the former showing the usual edema, hepatic damage, and changes in the skin and hair. Sickle cell disease is very frequent.

Interesting findings exist in the field of cardiovascular disease. Hypertension, often said to be infrequent in the African, is quite common in both men and women. Much hypertension throughout Africa is said to be based upon pyelonephritis. In the United States hypertension is looked upon as an important accelerating factor for atherosclerosis and therefore frequently accompanies coronary disease. The latter, however, is quite infrequent in Ghana, a fact confirmed by an inspection of the autopsy records of the past five years in the Korle-Bu Hospital in Accra. The situation is similar to that reported in Japan where hypertension is frequent and again coronary disease is not a common accompaniment. Whether dietary or other factors present in our country and absent in Ghana act as conditioning agents when hypertension accelerates the coronary damage is not clear. However, here is a relationship in disease in which "geographic" medicine both in the epidemiologic approach and in the laying of the groundwork for detailed laboratory investigation may be profitable.

Cor pulmonale is more common in much of Africa than in our own country. Sickle cell disease and schistosomiasis both help increase the frequency of cor pulmonale. In Ghana it is estimated that 20 per cent of the population has schistosomiasis. Over 99 per cent of the population is Negro. Other factors may be active in the increased frequency of cor pulmonale as well. However, relationships are not clear.

Common in much of Africa, especially to the

east and south, but extending into Nigeria and West Africa as well, is so-called idiopathic hypertrophy of the heart. This entity or these entities differ from endomyocardial fibroelastosis as we see it in the United States. The endocardial thickening is apparently patchy and not as diffuse as fibroelastosis. The involvement of the elastic fibers is neither extensive nor uniform. Adult males are most commonly involved. The patients show clinical pictures of congestive heart failure and at times evidences of valvular incompetence. Unlike rheumatic heart disease the semilunar valves are usually intact. Systolic apical murmurs with thrills, an enlarged left atrium without mitral stenosis, a variety of EKG changes, at times unexplained hydropericardium and atrial fibrillation without clear-cut cause are among the clinically important findings. The cause is obscure. In south Africa Gillanders has described a similar picture with evidences of nutritional changes including liver damage. The picture is distinctly different from beriberi heart. In Nigeria eosinophilia has been described in some patients. It is possible that varying basic diseases are being described or that combinations of disease make up these pictures.

The above report indicates something of the health and medical problems of Ghana and the serious and difficult task facing that country. Much has been done in the past half century to improve the health status of Ghana and other West African territories An overwhelming job remains and now the attack is being transferred to the young new countries to carry on. Help from international groups, such as W.H.O. as well as other agencies, is vital. What the future holds is problematic and the fears are well expressed by K. R. S. Morris of the Liberian Institute, in a recent issue of Science (**132**: 652, 9 Sept. 1960). His concern about the maintenance of the advances in health already made in Africa, and future progress in this area as affected by the newly founded independent political units springing up throughout the continent, is worthy of the reader's consideration and of concerted action by those of us in a position to help. Morris points out that those working in Africa are confronted with a disturbing reversal of the past half century's progress in the conquest of disease in Africa. Petty nationalism now arising in the new African states, he continues, may produce effects not only serious to the new countries but to other territories as well, for eradication of disease cannot be based upon political boundaries. In African sleeping sickness, for example, success depends upon meticulous planning and action down to the smallest detail. However ready the new nations may be to follow precedent of interaction, it is unrealistic to expect them to achieve high standards and have proper resources for some time. Such agencies as W.H.O., capable of putting forward a realistic program on international lines, are now more important than ever.

The History of Opium[1]

By ARTHUR DICKSON WRIGHT, M.B., M.S., F.R.C.S.[2]

OF THE drugs in the Pharmacopeia, opium is the most hypnotic, the most magnetic, and, it seems, the most potent of them all. Thomas Sydenham was enthused three hundred years ago when he wrote:

"Here I cannot but break out in praise of the Great God, the giver of all good things, who hath granted to the human race as a comfort in their afflictions no medicine of the value of opium, either in regard to the number of diseases it can control or its efficiency in extirpating them. Medicine would be a cripple without it and whoever understands it well will do more with it alone than he could well hope to do from any such medicine."

Opium still reigns supreme in its power to relieve pain, and the above tribute is especially appropriate since Sydenham prepared the early alcoholic extract known as "wine of opium". Contrary to Sydenham's views, however, its curative powers are poor except in paralytic ileus and diarrhea, but it does give relief from tormenting pain and this allows Nature time to rehabilitate the patient. Doctor Samuel Johnson, tortured by nocturnal cardiac asthma, expressed it thus:

"I need not tell you that opium cures nothing, though by setting the powers of life at ease, I sometimes flatter myself that it may give them time to rectify themselves."

For the treatment of incurable malignant disease it is God's own blessing; nearly all such sufferers die addicted to it and grateful to it. As a suicidal agent, however, it has declined in favor of the barbiturates, but before they were available it was quite fashionable, possibly because it was so often ineffective. That trio of friendly addicts—Baudelaire, Shelley, and Edgar Allan Poe—all attempted suicide with it—ineffectively.

Like all of God's good gifts, it has been abused and has brought besides its blessings much abuse and consequent misery in its train. It led to four wars, two of which were described as the "opium wars", with China, the object of which was to make the Chinese accept the import of Indian opium as a return cargo for their tea and other goods. Britain was thus led into one of its lowest points in political morality over these two wars, for which both overweening Disraeli and unyielding Palmerston later expressed regret, with which regret Gladstone naturally concurred. The first was from 1839 to 1842, and terminated with the Treaty of Nanking; the second was from 1857 to 1860, and did not quite terminate with the Treaty of Tientsin in 1858, but smouldered on until Lord Elgin ended it by burning down the Emperor's Summer Palace at Peking.

The other war in which opium was involved was the Conquest of India by Lord Clive, ending with the Battle of Plassey in 1757. One of the glittering prizes of this conquest was the opium trade with China, laboriously built up by the Portuguese and the French. The Indian mutiny at Sepoy in 1857 was generally attributed to the grease on the cartridges, suet for the Hindoos and lard for the Mohammedans. It is likely that the real cause was the dispatch of Indian troops overseas to the China war, a proposal contrary to their religious tenets, just as much as was the grease on the bullets.

Furthermore the segregation of land for opium growing, which was fostered by the government of India, took away much soil from the productivity of India and played a part in bringing on the great famines. The cat-

[1] Kate Hurd Mead Lecture in Medical History XIII, Woman's Medical College of Pennsylvania, College of Physicians of Philadelphia, 21 February, 1961.

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astrophic Persian famine of 1870 was also attributed to opium growing.

The morale of nations has been degraded by opium addiction, as in China and Egypt, and even in America there is cause for anxiety, especially with reference to addiction among adolescents, and there are now federal hospitals for addicts in Kentucky and Texas.

The actual discovery of opium is obscure, but there is little wonder that it was discovered in the great hunt for herbal remedies through the ages. As a child, I remember how attracted I was by the brilliant flower quickly changing to a large seed case oozing latex when scratched and drying to a rattling shell from which the spherical seeds could be scattered by the wind or by hand. These seeds I found on my bread and biscuits, and later heard of their oil with the attractive name of sesame.

Opium was probably first discovered and used in ancient Greece, near the commencement of the Christian era. Its origin was the white poppy of the Middle East, *Papaver Somniferum*. John Keats spoke in his *Ode to Autumn*, of that season being, "on a half-reaped furrow sound asleep, Drows'd with the fume of poppies". Later, other opium-yielding variants were cultivated, purple petals and purple seeds in Persia, and red petals and black seeds in India.

Vague early references are found in the Ebers Papyrus (1500 B.C.), where a mixture of opium pods and fly excreta was used as a sedative for children. In Grecian mythology, Demeter used poppy to drown her sorrow for her daughter, Persephone, abducted by Dis. Socrates knew of opium, but preferred hemlock at the end.

Theophrastus, the Greek botanist, mentions poppy as an emetic and anticonvulsant and Heraclites seventy years later praised it as an anodyne. The Bible also has vague but probable references to opium. Its use came with Greek culture to Rome and is mentioned by the Latin poets Vergil and Ovid. Celsus, in 25 A.D., recommended it strongly, and Scribonius Largus in 40 A.D. described the method now used for obtaining the latex. Pliny differentiated between the latex from pod-opium and the extract of the whole plant—called *meconium*—noting that the first was the better. Dioscorides (80 A.D.) gave a clear account of its use and Galen stressed its tendency to addiction, citing the case of the Roman Emperor Antoninus.

After the decline of Rome, the next mention of it is in Arabia and Persia. From Arabia, opium made its way to India and China in the Sung dynasty and later the Portuguese took over the trade, then the French, and finally the British.

In surgery, opium was first used by Hugh di Lucca, of Italy, and John Arderne, of England. The latter, the first specialist-proctologist of all time, described complicated methods for its use in painful rectal conditions, recognized it as a dangerous poison, and gave methods for resuscitation of the overdosed patient. Paracelsus, in the fifteenth century, named his tincture of opium *laudanum*. This brings us back to Sydenham, who, with his convenient wine, gave the use of opium a great impetus. Sydenham's pupil, Thomas Dover (1660–1742), a physician and buccaneer, incorporated a huge dose of opium in his famous powder.

In literature there are many references to opium in olden times. Boccaccio, himself a medical doctor, probably refers to the use of opium when discussing the amputation of a leg by the Maestro Mazzea, who was supposed to have been so impressed with its potency that he gave a dose to his wife's admirer with the desired result. Chaucer mentions 'fine opium of Thebes' as being used to facilitate the escape of Palamon in "The Knight's Tale", first of *The Canterbury Tales*.

Shakespeare mentions it in *Othello* (act III, scene 3, lines 330–333):

"Not poppy, nor mandragora, Nor all the drowsy syrups of the world
Shall ever medicine thee to that sweet sleep
Which thou ow'dst yesterday."

The cult of the opium-producing poppy spread by Arabian dhows to India and from there to China—which was destined to become the greatest consumer of all. The Portuguese in

their Eastern trade found it a useful article of commerce in the trade between India and China, using it as a return cargo in ships carrying Chinese products to India. During the French ascendency in India, the opium trade grew and was one of the glittering prizes which Hastings and Clive secured for Britain when they conquered India in the eighteenth century.

The trade was made a government monopoly by the British in India and was fostered in every possible way. Quantities shipped to China grew to nearly 10,000 tons annually (1,000 tons of morphine), bringing in a taxation revenue of £9,000,000 and a gross value of £20,000,000. China was at the same time both avid and reluctant to receive it, and when the Chinese Government forbade its import, hulks were anchored off the Chinese coast from which the smugglers drew their supplies—an episode reminiscent of Prohibition schooners off the U.S. coast. The Emperor Tao-Kwang in 1839 sent his strong man Commissioner Lin Tse Su to stop the trade. When Lin burnt the hulks, £2,000,000 worth of opium smoke drifted across Canton in the holocaust. (This resembled an earlier action in Boston against another drug—tea—which led to the American War for Independence.) This action led to the first opium war between Britain and China, which ended with the Treaty of Nanking in 1842.

Further opium troubles caused the second opium war of 1857 which ended with the Treaty of Tientsin in 1858. The action of Britain in obtaining income from opium (to finance its development of India) by encouraging Chinese addicts did not pass unnoticed in England, where a 'Society for the Suppression of the Opium Trade' was created under the presidency of that great humanist, the Earl of Shaftesbury (1671–1713), who is remembered in London today by Shaftesbury Avenue and the Eros of Piccadilly—endeavoring to bury its shaft into the ground. Violent meetings took place in which the opposition held that opium smoking was a harmless habit, described by Sir George Bentwood as "innocuous as twiddling one's thumbs". Others contended that opium addiction was much less evil than alcoholism, with its stages of excitement and violence preceding coma, for opium sends one gently to sleep without the preliminary wife-and-children-beating stage.

The opium trade was the main source of revenue in Malaya during my sojourn there. A government factory poured out endless supplies of the black treacle to the Chinese laborers on pieces of dried banana leaf and later in tooth paste tubes. Scattered through the town were the government opium shops with open doors through which one could see the tiers of wooden bunks with smoking and sleeping individuals recumbent on them. Europeans were not admitted to these shops, but all others were welcome. At a rich man's dinner it was conventional to have an opium couch for the guests after dinner. A a small boy servant would dexterously roll an opium pill for the guest by roasting the opium treacle on a small wooden sliver over an oil lamp until a pill the size of a pea was produced which was then placed on the orifice of the opium pipe (which has no bowl as does a tobacco pipe). Through the hole left by the wooden sliver, the flame of the oil lamp is drawn in and quite soon the opium sizzles and becomes a ball of gray dross and the inhalor has a nice sleep enlivened by visual dreams wonderfully described by Baudelaire as "the phantom forms that haunt the deep caverns of the soul".

The great mystery of it all is that the dross contains 9% of morphine which the addict next eats; if left, the boy puts it into a match box and the next day sells it to the Government for its morphine content. It is then mixed into new opium to make further supplies for the opium shops. Only 1% of the morphine is sublimated up the pipe; much of that is chemically altered by the heat and the rest is deposited on the walls of the pipe, so what produces the effect on the smoker, one may ask? Possibly degeneration products exert a powerful effect. Research is still required into the combustion products of opium; maybe there are new drugs there of great value, especially in the realms of psychopharmacology.

My sole excursion into opium smoking produced nausea and vertigo which drove me out of the house of my charming host without the courtesy of saying thanks and good night. It was reminiscent of my first and last experiment with a cigar, both of which experiences convinced me that there is nothing of Thomas de Quincy or Sir Winston Churchill in my make up!

It is interesting that in India opium is not smoked, but eaten. In Persia and China it is smoked, while in countries of culture and refinement, like England, France, and America, it is purified and injected subcutaneously as a solution of its main constituent, morphine, or of its more attractive derivatives, heroin or pethidine. An addict may present the front of his thighs studded with the blackheads produced by morphine injections given through the trousers or, if in public, through the trouser pockets. It is puzzling why women seem to prefer injections in the buttocks, where, in the female addicts, 'fly marks' abound. Do they give it to themselves or do their consorts in vice do it for them? I have observed that drug addiction is often shared with one of the opposite sex. Pethidine, incidentally, is not well tolerated by the tissues. Morphine never produces the abscess which is a frequent and sometime fatal occurrence with pethidine. Moreover pethidine often produces a leathery, puckered skin which, on the abdominal wall, can make surgical incision difficult.

Opium was an herbal remedy until Friedrich Wilhelm Adam Sertürner (1783–1841), the apothecary of Paderborn, Westphalia, obtained morphine crystals from opium extracted with glycerol (a weak acid) and heated with ammonia. By separating these crystals in the year 1806, he became the pioneer of all the alkaloids, as Sir Alexander Fleming was to become the pioneer of all the antibiotics over a century later. Sertürner isolated morphine and tried it on his friends and himself, with near-fatal results. This work, isolating the first alkaloid, was an important discovery. Following this isolation, twenty-one more alkaloids were discovered in the latex of the poppy head. Many of them exhibited entirely different properties from those of opium; some were even convulsants. Only two of them have served medicine separately but quite usefully, codeine for migraine and sciatica, and papaverine as a vasodilator in heart and vascular disease. The name *codeine* comes from *kodeia*, the Greek word for "poppy head", and the label *papaverine* honors the poppy genus.

The culture of the opium plant, *Papaver Somniferum, Sp. Arabim*, is of great interest. This plant probably was first grown in Turkey. It has a white flower and white seeds, with a huge seed capsule, of 1½ inch diameter. The white flowers throve in China where vast areas were cultivated to compete with Indian imports. Chinese politicians then executed the usual violent dialectical acrobatics by leaning over backwards to explain the morality of this behavior, after vociferously resisting British importation of the vile drug.

The poppy plants are put down in November, following the reaping of the earlier nutritional crops which are much less remunerative. They are subject to many diseases and the harvest is jeopardized by wind, rain and cold. The collection is very laborious and the moment is chosen by color blanches produced by pressing on the seed capsule. The seed capsule is then scarified by a multi-bladed knife, like an old time wet-cupping scarifier. This incision is generally made in the evening and the inspissated latex removed the next morning. The method of scarification of the seed cup varies: vertical in Turkey, oblique in Persia, and transverse in India. The capsules are scarified daily for six days. The latex is scraped off with a small iron spoon, shaped like a trowel, which is kept moistened with saliva, sweat, water or oil to prevent the latex from adhering. The contents of the spoon are transferred from time to time to a metal bowl. A man working all day can only obtain about ten ounces of opium, so cheap labor is a necessity. The crop also realizes other returns; the flower petals are glued together with a substance called leva, which consists of a fluid exuded from the opium (prissewah) and another

fluid from washing the opium vessels. The petal paper so obtained is used for wrapping the opium balls for export. Poppy 'trash' is a second return, and consists of dried leaves, stalks and capsules. This is used for packing the opium balls and it in turn contains some opium for the factories in distant China. The last product, poppy seeds, yield 40% of sesame oil and these are used in the confectionery trade. These seeds and their oil contain no opium. (The function of opium latex is to protect the growing plant from its enemies.)

The more fascinating side of the history of opium has been its effect on literature and the arts. Certain names have already been mentioned; nearly all these sufferers had a valid excuse for opium-taking, and many of them had medical training and contacts. The English poet George Crabbe (1754–1832) practiced as an apothecary at Aldeburgh and took opium for his Menière's disease. He later was ordained in the Church of England, a beloved man. Crabbe never gave up opium, taking it until his death at age seventy-seven.

Samuel Taylor Coleridge's brother Luke was a medical student at the London Hospital, and Coleridge grew up immersed in medical lore; he could recite Blacard's *Dictionary of Medicine* page by page. His excuse for taking opium was rheumatic fever, contracted while a student at Christ's Hospital by going swimming in his clothes. He started the drug at nineteen with 'Kendal's Black Drop', a form of paregoric (camphorated tincture of opium) which gave him wonderful relief for his arthritic pain and swelling. (Paregoric derives its name from the Greek word meaning "consoling"—appropriate, in a sinister way, for a drug which can lead to opiate addiction.) Coleridge took opium all his life, from age nineteen to sixty-two, drinking as much as one-half a pint of laudanum at a time. His last days were spent in a kindly doctor's home in Hampstead where his laudanum could be rationed. His postmortem examination revealed a hopelessly-damaged, huge rheumatic heart. Coleridge had life-long pain and suffering, so he took opium, "as a means of escape from pain that coiled around my mental powers as a serpent around the body and wings of an eagle. . . My sole sensuality was not to be in pain".

De Quincey had toothaches as an excuse. He took enormous quantities of opium for ten years (from age 27 to 37), then gave it up and lived to seventy-four. By his *Confessions of an English Opium-Eater* he led many thousands to addiction. Opium was a stimulant to his work, especially when he was escaping from its chains.

Sir Walter Scott's excuse was gallstone colic with jaundice; this side of his character has escaped study so far, except to explain the mystical beauty and words of "The Bride of Lammermoor", which stands head and shoulders above all his works, as if it was written by another man, and so it was—by a drugged man.

Francis Thompson was a doctor's son, a mystical Roman Catholic and for six years dilettante medical student at Manchester, spending his working days in public libraries in the chase of another drug—that of words and poetry. He also spent many hours watching that gentle anodyne and time-waster—cricket—a sport he gave up when in London, "where Lords and the Oval were poor substitutes for all to afford".

Poor Francis Thompson! His mother placed in his hands the *Confessions* of de Quincey; at the age of nineteen Thompson took to opium to escape the frustrations and cruelties of life. He sank into poverty as deep as did de Quincey and accepted the greatest indignity a man may accept, sponging on women, as did de Quincey. Thompson immortalized his encounter with addiction in romantic morphine-laden words.

Crabbe, Coleridge and Thompson, frail and helpless geniuses, eventually excited the pity of kind folk and so ended their days surrounded by loving friends. Crabbe with Edmund Burke, Coleridge with Doctor and Mrs. Sillman, and Francis Thompson with Alice Meynell and her husband. Their powers to resist gone, and, provided with room and sustenance, their morphine-inspired genius

left us mystical and deathless poetry—all with the odors of drug delusion and the vistas and panoramas of their dreams. "The long savannahs of the blue", of Francis Thompson, "The stately pleasure dome," of Kubla Klan, "where Alph the sacred river ran through caverns measureless to man, down to a sunless sea", which Coleridge saw after two grains of opium at Porlock, and the "traffic of Jacob's ladder/ Pitched betwixt Heaven and Charing Cross", which Thompson saw as he drowsed homeless and starving on the Embankment in London.

We have wandered with these poets, "down the arches of the years, . . . down the labyrinthine ways", and lingered with Shelley in, "Vast ruins in the midst were spread Pillars and pediments sublime/Where the grey moss had formed a bed/And clothed the crumbling spoils of time". At a distance we can enjoy these drug-addicted authors of the past as perhaps we enjoy the alcoholic playwrights of today.

Man still can find no substitute for opium. It is God's gift to suffering humanity now as it was in Sydenham's day. But opium has piled up a large reproach against itself: it has degraded nations, it has robbed individuals of all self-respect, but has left behind some memorable lines of prose and poetry. Although those that wrote them were conscious of their shame, they felt that in some way they rose above mundane mankind.

Did not Francis Thompson write?,

"I hang 'mid men my needless head,
And my fruit is dreams, as theirs is bread?"

There was, however, more humility in Samuel Taylor Coleridge as death drew nigh:

"O! Lift one thought in prayer for STC,
That he who many a year with toil of breath,
Found death in life, may now find life in death."

Edgar Allan Poe, drunk and drugged, stumbled about the streets of Philadelphia one hundred and thirty years ago and had doors slammed in his face when he applied for a humble post in the Customs Office. A sad genius, he returned again to his life of sponging on womankind. But his brain and pen left us some immortal poetry and prose. In Poe's poem, "For Annie", he mustered the courage for a little sardonic humor:

"And the fever called 'Living'
Is conquered at last.

. . .

But no matter!—I feel
I am better at length."

Rush and Physick: An Important Medical Friendship*

By GEORGE F. SHELDON, M.D.†

NO AMERICAN physician has been studied more extensively than Dr. Benjamin Rush. However, a neglected aspect of Rush is his close personal and professional relationship with the "Father of American Surgery", Dr. Philip Syng Physick.

Whether Rush and Physick were acquainted before Physick's return from John Hunter's school in London, in 1792, is unknown. The professional association of the two Philadelphians began during the great yellow fever epidemic of 1793. This plague decimated the populace of Philadelphia, and caused President Washington and Congress to flee the city.

Early in August of 1793, Doctor Rush had observed several cases of yellow fever which he at first dismissed as isolated cases. After conferring with his colleagues he decided that the fever was assuming epidemic proportions, a viewpoint severely criticized by his colleagues. Soon, however, the presence of a plague could no longer be denied. A "pest house" was established at Bush Hill and Doctors Physick, Cathrall, Annan, and Leib were appointed to staff it. Bush Hill, however, was located some distance from the city, and the doctors' visits were infrequent and brief. Conditions became deplorable, and two, merchants, Stephen Girard and Peter Helm took charge of the hospital. Among their first decrees was a demand for a resident physician at Bush Hill. Dr. Jean Deveze, a French surgeon, was appointed to this post, but his presence occasioned the resignation of Physick and others who disagreed with his views regarding the treatment of yellow fever.[1] Physick cannot be blamed for deserting Bush Hill as numerous citizens in Philadelphia relied on his aid and, as Rush mentioned in a letter to his wife, Physick contracted the disease.[2]

Disagreement concerning the etiology and treatment of yellow fever was not limited to the physicians at Bush Hill. Ignorance of the true nature of yellow fever gave rise to ludicrous theories of its etiology and treatment and split the ranks of Philadelphia medical men. Rush tried many methods of treatment before he settled upon his well-known regimen of a violent purge coupled with the copious letting of blood. Employment of this system prompted him to write on September 10, 1793, "Thank God, out of one-hundred patients whom I've visited or prescribed for this day, I have lost none."[3]

Rush's views, however, provoked great opposition among other physicians. The foremost of his foes was Adam Kuhn, whose treatment consisted of bark, camomile tea and cold infusions. The publication of these two radically different regimens rapidly divided the doctors into two conflicting schools, often labeled the "Rushites" and the "Kuneans".

Prominent among the "Kuneans" was Caspar Wistar, later the author of the first American textbook of Anatomy. Rush previously had referred most of his surgical cases to Wistar, and he considered the anatomist a firm friend. Upon learning of Wistar's failure to support him, Rush became angry and likened

* Read before the Section on Medical History, College of Physicians of Philadelphia, 15 November 1960.

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[1] *Minutes of The Committee of The Citizens—1793*, Philadelphia: (1848), pp. 12, 33.

[2] L. H. Butterfield, (Editor), *Letters of Benjamin Rush* (Princeton: 1951), p. 708. Letter from Benjamin Rush to Julia Rush, Philadelphia, October 8, 1793.

[3] F. R. Packard, *History of Medicine In The United States*, (Philadelphia: 1931), p. 139.

Wistar to Brutus.[4] Subsequently, when Rush's patients required surgical evaluation and treatment they were seen by Physick.[5]

Among the first to adopt Rush's method was Physick. His confidence in bleeding and purging had been partly responsible for his resignation from Bush Hill. He had come so completely under Rush's spell that he actively sided with him against Adam Kuhn, who had been Physick's preceptor from 1786 through 1788. His faith in Rush, however, met a sterner test; when Physick himself became ill, he submitted to Rush's system. It was quite natural that he should attribute his subsequent recovery to bleeding and purging.

Physick also agreed with Rush in assuming that the plague was not imported from the West Indies but of domestic origin. This view was challenged by Philadelphia physicians and laymen who saw such a possibility as a personal affront. Rush, always the crusader, vigorously defended his thesis, but the reticent Physick "neither talked nor wrote about it, except in monosyllables (and even in them only when interrogated), but was firm in his opinion".[6]

In 1793, Rush believed yellow fever to be contagious, a view Physick did not share: Dr. Charles Caldwell, a frequent antagonist of Rush, and later founder of a medical school at Louisville, wrote:

> In relation to his hypotheses, theories, opinions and doctrines, the general and almost uniform practice of Doctor Rush was known to be very often to change and even abandon them of his own accord; but never to do so from the influence of others. [Because of] arguments of Doctor Physick and myself [whom alone], for several years, he allowed to controvert his sentiments without taking offense at us—and at Doctor Physick, he never took offense—under our influence . . . he relinquished his belief in the contagiousness of yellow fever . . .[7]

Physick, according to Caldwell, usually did not contest a point with Rush even though they were in disagreement. Physick's deference to Rush was probably the clue to their long friendship and, conversely, was the reason Caldwell and Rush were not friendly in later years.

Physick, however, worked closely with Rush before his illness. When Caldwell became ill with the fever they were called to his bedside. His description of this meeting with the two friends illustrates the personality traits of this pair and provides insight into their unique partnership.

> On entering my chamber, Doctor Physick, one of the most single-hearted and unostentatious of men, took me by the hand, gave me a frank and friendly salutation; and with him, there the ceremony ended. But not so with Doctor Rush; he, though with unusual gentleness of action . . . exercised toward me the whole resources of his amenity and courtesy [and] paid me some of the most high-wrought but delicate compliments his fancy could frame.[8]

Caldwell asked that their consultation be conducted in his presence, and at this unusual request, "a significant look . . . passed between [Rush] and Doctor Physick" for they felt he must be delirious to ask such a favor. They agreed and Caldwell ultimately recovered[9]. As his views coincided with those of Rush and Physick, to a limited extent, he supported their efforts. Caldwell along with Rush and Physick, agitated for the introduction of Schuylkill water into the city as a public health measure. This project was adopted in 1797 and completed in 1801, but was eventually abandoned for a more economical plan.[10]

Although Physick supported Rush's public health measures, he was more interested in studying the pathogenesis of yellow fever. While at Bush Hill, he performed numerous *post-mortem* examinations on yellow fever

[4] L. H. Butterfield, *op. cit.*, p. 752. Letter from Benjamin Rush to Julia Rush, Philadelphia, October 31, 1793.

[5] Charles Caldwell, *A Discourse Commemorative of Philip Syng Physick*, M.D., Louisville, Ky., 1838, p. 17.

[6] Charles Caldwell, *Autobiography of Charles Caldwell, M.D.*, (Philadelphia, 1855), p. 253.

[7] Caldwell, *Ibid.*, p. 286.

[8] Caldwell, *Ibid.*, p. 281.

[9] Charles Caldwell, *Ibid.*, p. 282.

[10] Middleton, W. S., "Charles Caldwell, A Biographic Sketch", Journal of Medical Education, October, 1959, p. 973.

victims and is credited by Caldwell with popularizing the practice among his colleages. Physick was perhaps the first to demonstrate the gastric effects of yellow fever; these findings certainly preceded Broussais's similar conclusion.[11]

Rush faithfully recorded Physick's observations and modified some of his views concerning yellow fever as a result of them. In 1793, Rush noted:

> Frequently on the fourth or fifth day, a discharge of matter from the stomach resembling coffee impregnated with its grounds [was observed] but subsequent dissections by Doctor Physick have taught me that it was the result of those morbid actions in the stomach which afterwards produced the black vomit.[12]

He also recorded Doctor Physick's observation that no "morbid" changes occur, if the patient dies early in the disease."[13]

Although Physick's autopsy studies instructed Rush, his clinical observations were less enlightening. Rush records that:

> An acute pain in the eye, Doctor Physick informed me, produced the symptoms of what is called a putrid fever, which terminated in death in five days. [Physick had seen this patient while under Hunter's supervision] in St. George's Hospital in the year 1789.[14]

He further wrote, "Doctor Physick informed me that in one of his patients the pulse was reduced in frequency to thirty strokes in a minute," an observation completely without value.[15] It is commendable that these two physicians, particularly Physick, tried to base their understanding of yellow fever on the scientific validity of a *post-mortem* examination. Their tendency, however, to overemphasize physical signs merely resulted in the perpetration of erroneous theories of etiology and treatment.

In spite of their extensive studies, Physick and Rush had not convinced Adam Kuhn and his supporters. Winter ended the plague of 1793 with the "Rushites" and "Kuneans" still in disagreement.

The conflict concerning yellow fever might have been peaceably resolved if the common enemy had not reappeared in 1794. On June 6 of that year, the first newly recognized case of yellow fever was reported to Rush by Physick.[16] Sporadic outbreaks occurred throughout June and July. By August of 1794 a severe epidemic raged.

On August 29, Rush was invited to attend a meeting of the Board of Health.[17] He told the members of all the yellow fever cases he and Physick had attended since June 9 and recommended measures to avert a disastrous epidemic. The Committee, however, rejected his advice and invited the city's physicians, except Rush and his two friends, Physick and Dewees, to appear before them at city hall. The physicians and Board of Health then united in declaring that there was no reason to fear an outbreak of yellow fever.[18]

These proceedings were an insult to Rush, who immediately took up the challenge. On September 13, 1794, he sent to the Committee of Health a memorandum which included several recommendations and a reply to his enemies. In this letter Rush expressed his modified view that the fever was contagious. Rush also outlined his well-known treatment and charged his opponents with minimizing the danger by calling the disease by less fearsome names. To bolster his declining prestige, he concluded by stating that Doctors Physick, Barton, and Dewees concurred with him in these recommendations.[19] Most Philadelphia physicians, however, followed the leadership

[11] Francois Broussais (1772–1838) a distinguished French physician who like Physick believed the gastrointestinal tract to be the site of the primary lesion in yellow fever.

[12] Benjamin Rush, *Medical Inquiries and Observations*, (Philadelphia: 1809), Vols. I–IV, **3:** 110, 111.

[13] Rush, *Ibid.*, **3:** 106.

[14] Rush, *Ibid.*, **3:** 44.

[15] Rush, *Ibid.*, **3:** 98.

[16] Rush, *Ibid.*, **3:** 359.

[17] Benjamin Rush, *Ibid.*, **3:** 364.

[18] F. R. Packard, *op. cit.*, p. 142.

[19] L. H. Butterfield, *op. cit.*, p. 749, Letter from Benjamin Rush to the Committee of Health, Philadelphia, Sept. 13, 1794.

of the College of Physicians, which denounced Rush's conclusions. His disciples dwindled. He wrote on December 19, 1794, that although Doctor Kuhn's lectures on yellow fever were evoking laughter from his own students, Kuhn remained the "Apollo" of the College of Physicians.[20]

Despite the unpopularity of their theories, Rush and Physick continued to study the disease. They were now thoroughly convinced of the superiority of their treatment. During a short period Rush had treated one hundred and twenty cases and had lost only two. Alternative remedies they regarded with deeper suspicion than previously. They observed that bark was "except in two instances without success; and in them did not take effect until after bleeding".[21]

Believing that his system could be applied successfully by anyone, Rush could not understand why more physicians did not adopt it. He noted that Physick was having unparalleled success and wrote:

> The anti-phlogistic remedies were not successful in Philadelphia in the yellow fever, in my hands alone. They were equally, and perhaps more so, in the hands of my friends, Doctor Giriffitts, Doctor Physick, Doctor Dewees, and Doctor Woodhouse.[22]

Physick convinced Rush of his adeptness when he saved two patients "by drawing above one hundred twenty ounces of blood from them".[23] Another patient, treated by Rush and Physick, had been "cured by plentiful bleeding and purging, but relapsed [and] expired in a fainty fit".[24] They had done their best for him.

The strain of the plague exerted a telling effect on Rush. He felt that all disease appeared more severe in 1794. Physick's observations seemed to confirm this belief for he had told Rush of two "Puerpile" cases which presented with symptoms "more violent" than usual.[25]

In 1795 yellow fever did not appear in epidemic form, but intermittent outbreaks of the disease occurred. Rush concluded that wine hindered treatment in these cases because it had triggered a relapse in one of Doctor Physick's patients. Another yellow fever patient whom they visited developed pleuritic symptoms and died.[26]

Physick's steadfast allegiance throughout the yellow fever controversy caused Rush's affection for him to deepen. Rush proudly noted, in 1795, that Physick exceeded even him in blood-letting.[27] In March 1795, Physick asked Rush to visit a patient with him. She lay sick with a fever; Physick had bled her four times. Rush noted:

> . . . in this alarming state I suggested nothing to Doctor Physick, but to follow his judgment for I knew that he was master of that law of animal economy which resolved all her symptoms into an oppressed state of the system. The doctor decided in a moment in favour of more bleeding.[28]

Physick not only subscribed to Rush's controversial methods but also found new use for them. Rush recorded a "principle" applied by Doctor Physick in the reduction of a bone dislocated two months previously; in this case, Physick bled the patient until he fainted and then speedily reduced the shoulder. Rush happily noted that this procedure then became standard practice in Philadelphia.[29] Although Physick later made significant contributions to orthopedic practice, this crude precursor of anesthesia can scarcely be listed among them.

Although Physick supported Rush, he avoided implication in his friend's quarrels.

[20] Butterfield, *op. cit.*, p. 753, letter from Benjamin Rush to John Redman Coxe, Philadelphia, Dec. 19, 1794.

[21] Benjamin Rush, *op. cit.*, **3**: 415.

[22] Rush, *op. cit.*, **3**: 426.

[23] L. H. Butterfield, *op. cit.*, p. 752. Letter from Benjamin Rush to John Redman Coxe, Philadelphia, November 4, 1794.

[24] Rush, *op. cit.*, **3**: 422.

[25] Rush, *op. cit.*, **3**: 389.

[26] Benjamin Rush, *op. cit.*, **3**: 418, 419.

[27] L. H. Butterfield, *op. cit.*, p. 765. Letter from Benjamin Rush to John Redman Coxe, Philadelphia, Dec. 8, 1795.

[28] Rush, *op. cit.*, **4**: 311.

[29] Rush, *op. cit.*, **4**: 378.

Rush's clientele suffered as a result of his altercations, but Physick's practice, meager before 1793, grew rapidly. His reputation as a surgeon spread throughout the country. Rush faithfully documented Physick's success and observed in 1794, "that Doctor Physick is rising into great business".[30] By 1796, Rush concluded that Physick's success was due to the excellent location of his office and his adoption of the "new principles in medicine".[31] A more accurate reason for Physick's success, however, was probably his stature as a surgeon.

The respite from yellow fever ended in 1797, but the battle against disease loomed small when measured against the strife among factious Philadelphia physicians. Rush and his disciples again formed one camp, but the anti-Rushites were now led by William Currie. The disagreement centered mainly on different concepts of the origin and treatment of the disease. The argument reached such a pitch that Rush was even challenged to a duel.

As in earlier epidemics, the College of Physicians opposed Rush's heroic treatment. This group's disapproval had led Rush to resign from its membership in 1793, even though he had been one of the College's founders. Philadelphia officials usually needed the collective advice of this distinguished organization instead of the disorganized protests of Rush and his more laconic followers. Tired of warring against the College alone, Rush organized his followers into a society designed to refute the arguments advanced by the College of Physicians. Thus was born the Academy of Medicine of Philadelphia. Rush's constant friend, Philip Physick, became its first President. Although Rush prophesied success for the Academy, it was defunct shortly after his death. Physick faithfully never became a fellow of the College of Physicians.

Yellow fever and arguments concerning it were not Rush's only problems. Among his patients was Physick, who came to him with a toothache.[32] This toothache turned out to be a premonitory symptom of yellow fever.[33] Physick was treated according to Rush's regimen. After his convalescence Physick, who was now President of the Academy, spoke even more ardently in support of Rush's system. On September 14, 1797, the "Gazette of the United States" printed a testimonial from Physick:

> With a view of inspiring conficence in blood-letting, I take this method of informing my fellow citizens that I lost during my late attack of that fever, 176 ounces of blood by twenty-two bleedings in ten days. The efficacy of this valuable remedy was aided by frequent and copious evacuations from my bowels and a moderate salivation.[34]

With the winter "recess" from yellow fever, Physick and Rush began other studies. On February 27, 1797, they offered to assume responsibility for every mental patient in Pennsylvania Hospital who was not the particular charge of another physician, an offer promptly accepted by the hospital board and physicians.[35] Rush's studies culminated in 1812 in his important book on mental disease which for many years was the major American textbook on the subject. It is difficult to imagine the practical Physick studying the ethereal concepts of psychiatry. He probably joined Rush in this effort purely out of friendship.

The second greatest yellow fever epidemic of the 1790's struck Philadelphia in late summer of 1798. The Academy of Medicine and College of Physicians began lobbying for acceptance of their respective recommendations before the Board of Health and in the lay press. The College submitted its suggestions on the 6th of August and Doctor Physick, the Academy's President, forwarded that

[30] L. H. Butterfield, *op. cit.*, p. 753. Letter from Benjamin Rush to John Redman Coxe. Philadelphia, Dec. 19, 1794.

[31] Butterfield, *op. cit.*, p. 769. Letter from Benjamin Rush to John Redman Coxe. Philadelphia, Jan. 16, 1796.

[32] Benjamin Rush, *op. cit.*, **4:** 13, 36.

[33] Although it is known that an attack of yellow fever confers lifelong immunity, Physick felt that he contracted the disease twice (1793, 1797).

[34] Nathan G. Goodman, *Benjamin Rush*, (Philadelphia: 1924), p. 107.

[35] Thomas Morton, *A History of the Pennsylvania Hospital*, Philadelphia, 1895, p. 144.

group's recommendations on August 9. Neither system proved very efficacious and the acrimonious squabbles of the physicians caused the sick to distrust their advice. Accordingly, on August 13 the Board urged all patients to seek aid at the newly opened City Hospital to which Doctors Physick and Cooper were appointed managers and "whose professional eminence would ensure just confidence". Results and patients were slow in arriving, and the two managers asked Rush to recommend the best plan of treatment.[36] Physick, of course, must have anticipated the answer. Rush advised bleeding and purging.[37] A letter from Physick on September 7, 1798, to William Jones, Chairman of the Board of Health describes conditions at City Hospital and shows that Rush aided Physick in his efforts there:

> I very much fear that the time required to finish the building will prevent it from being of much use this year and as more room is absolutely necessary immediately it will be proper to have huts or a long shed put up in the roughest way—
>
> If these cannot be made quickly tents should be sent out and put up because some of our rooms are so crowded that the patients suffer exceedingly from bad air—Then there is a morass near the Hospl. which might be drained very easily by digging a well in the middle of it and [by] having this done would save us from breathing a great deal of very noxious air.
>
> Doctor Rush who came to y'Hospl this morning has mentioned and very strongly advised an immediate attention to these circumstances—I remain with [this] protest. . . .[38]

Rush, as a consultant physician to City Hospital in 1798, states that subjects for his study of yellow fever "were not only private patients, but the poor in the city hospital, who were committed to the care of Doctor Physick and myself by the Board of Health"[39] Rush's knowledge of the morbid anatomy "was communicated to [him] by [his] friend, Doctor Physick", who did many autopsies at City Hospital.[40] They noted that hoarseness, probably terminal râles, indicated a poor prognosis. However, Physick did tell Rush of a patient whose carious teeth interfered with treatment.[41] This case, and others, indicate that Rush, who is sometimes credited with the theory of focal infection, studied this phenomenon with Physick.

City Hospital was a more efficient institution in 1799 than in 1798 because more quarters were available and fewer citizens were afflicted with yellow fever. In that year Rush and Physick were joint managers of the infirmary. Although their radical cure was employed in City Hospital, the suspicious Board of Health made available to them a "miracle" drug which had been used in Germany. The two doctors, conservative in spite of their heroic treatment, rejected Doctor Bölke's "cure" for they did not know its contents.[42]

The first period of Rush and Physick's association ended with the last of the great yellow fever epidemics of the 1790's. During this period Rush's writings indicate that Physick, his junior by twenty-two years, was first his follower, then his friend and associate, and finally his equal.

After 1800, Rush clearly regarded Physick as superior in some forms of medical practice. He recorded many of Physick's observations, but seemed to overlook the great surgeon's soundest innovations. Rush failed to document

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[36] One letter (August, 1798) sent to Physick and Cooper by Rush acknowledged the uncertainty of any precise method of treatment in all cases and suggested that bleeding and purging were not always indicated. This letter was used as evidence for the defense during Rush's libel action against the pamphleteer, William Cobbett, who labelled Rush a "Sangrado" and suggested that his medical system contributed to the "depopulation of the Earth". *See A Report of an Action for a Libel, Brought by Dr. Benjamin Rush Against William Cobbett, in the Supreme Court of Pennsylvania,* December Term, 1799. T. Carpenter, Court Stenographer, Philadelphia, 1800.

[37] F. R. Packard, *op. cit.*, pp. 151–152.

[38] Ms, letter from Philip Syng Physick to William Jones, Esq., City Hospital, Sept., 7, 1798. Historical Society of Pennsylvania.

[39] Benjamin Rush, *op. cit.*, **4**: 68.

[40] Rush, *op. cit.*, **4**: 75.

[41] Rush, *op. cit.*, **4**: 82.

[42] L. H. Butterfield, *op. cit.*, p. 879. Letter from Benjamin Rush to Timothy Pickering, Philadelphia, Sept. 24, 1799.

Physick's famous seton operation for ununited fracture which he performed in 1802, but did note his erroneous conclusions concerning hydrophobia as well as Physick's trial of turpentine as an anti-emetic agent. Perhaps the rabies case particularly impressed Rush because the patient had been his and Physick had consulted with him, and finally had directed his nephew, John Syng Dorsey to perform an autopsy.[43]

Physick was on firmer ground when treating skin disease. Indeed, by the use of adhesive "plaisters" and bed rest he very nearly cleared the Pennsylvania Hospital wards of chronic ulcer cases shortly after his appointment in 1794.[44] Rush noted "this remedy had been used with great success by Doctor Physick".[45] On April 27, 1804, Rush prescribed a skin ointment for a patient and assured the anxious individual that he and Doctor Physick saw no danger of cancer.[46] Another case of this nature is described in one of Rush's letters.

> Soon after I received your letter I put it into the hands of my learned and ingenious friend Doctor Physick, who being unusually hurried at the time, was unable to consider fully its contents until lately, when we have met, and consulted on your case, I agree, that your disease in your neck is not that described by Mr. Pott, but the effect of the weakness induced by the weight upon your head (mentioned in your letter) and a Rheumatic affection in consequence of it. The remedy upon which we rely chiefly for a cure is a Caustic applied to your neck, and kept open for two or three months. Its efficacy will be aided by the use of such medicines as *reduce*, or *brace* your system according to the state of your *pulse*.[47]

This letter is quoted at length for it illustrates beautifully the cooperative efforts of Rush and Physick. The use of caustics in the manner described was a favorite remedy of Physick. Added to this practical treatment were Rush's theoretical notions of "systems and irritability".

Rush, however, referred his surgical cases to Physick and in turn managed Physick's purely medical cases. In 1804, Rush wrote to a rural practitioner:

> You have left me nothing to advise in the case of Col. Agnew, but his coming immediately to Philadelphia, and first consulting Doctor Physick who is at the head of the surgery of our city.[48]

They were regarded as a team to such an extent that Rush once received a remittance for "visits in the night in consultation with Doctor Physick".[49]

The citizens of Philadelphia were not the only ones to know of their association and receive the benefits of it. Famous Americans sought their aid. James Monroe requested a consultation between them in the case of his daughter, but was informed that she was hopelessly ill.[50] John Adams requested Rush's advice for his daughter, who had developed a tumor. Rush felt that surgery was indicated and to allay her fears wrote to Adams:

> . . . two years ago [I] had a tumor of perhaps larger size cut out by Doctor Physick from my neck. I was surprised when the doctor's assistant told me the operation was over and could not help saying after Caesar when he had finished his conquests, 'And is this all' ".[51]

The letter to Adams shows that Physick as Rush's personal surgeon, held the full measure of his confidence.

They also gave medical service to each other's families. In a letter to Physick's brother, Rush stated:

[43] Benjamin Rush, *op. cit.*, **2:** 350–354.

[44] Jacob Randolph, Memoir of P. S. Physick, M.D., (Philadelphia: 1839, pp. 40–41).

[45] Benjamin Rush, *op. cit.*, **1:** 394.

[46] L. H. Butterfield, *op. cit.*, p. 879, letter from Benjamin Rush to David Howell, Philadelphia, April 27, 1804.

[47] Ms., No. 29, Fugitive Leaves from the Library of the College of Physicians of Philadelphia, April, 1959. Letter from Benjamin Rush to Samuel A. Law, Esq., Philadelphia, March 5, 1803.

[48] Ms., letter from Benjamin Rush to Dr. John McCleland, Philadelphia, July 11, 1804. Historical Society of Pennsylvania.

[49] Nathan G. Goodman, *op. cit.*, p. 156.

[50] L. H. Butterfield, *op. cit.*, p. 1082, letter from Benjamin Rush to James Monroe, Philadelphia, June 1, 1811.

[51] Butterfield, *op. cit.*, p. 1104, letter from Benjamin Rush to John Adams, Philadelphia, Sept. 20, 1811.

> I consider myself a debtor to your worthy brother [for] many medical services rendered [to my] family. I cannot therefore accept of your handsome fee without doing especial violence to the dictates of justice, and of my own feelings.[52]

Physick himself had been treated according to Rush's recommendations, if not actually by him, when ill with yellow fever. In addition to his brother, Physick's father had been cared for by Rush when stricken with yellow fever in 1804, but "died on the seventh day with a red eye, hiccups and black vomiting."[53]

This unusual duo contributed most as pioneers of early medical education and inspirers of young men. Rush became Professor of Chemistry in the Medical Department of the College of Philadelphia in 1769, but in 1774 left the faculty for service in the Continental Congress and the Revolutionary cause. He returned to the faculty after the war—the College of Philadelphia had been amalgamated with the University of Pennsylvania by this time—and in 1796 became Professor of the Institutes and Clinical Medicine.

It was quite natural that he should encourage Physick to become a teacher. In 1800, a group of medical students from the University of Pennsylvania, desiring to learn more surgery than the inadequate offering in their curriculum, petitioned Doctor Physick to lecture in Pennsylvania Hospital.[54] Physick, apprehensive about the task, was encouraged by Rush, who attended his inaugural address. After Physick's lecture, Rush hurried to the platform and said while grasping his hand, "Doctor, that will do—that will do. You need not be apprehensive as to the results of your lecturing—I am sure you will succeed.[55]

Physick's teaching experience at the Pennsylvania Hospital prepared him for his most important appointment which came in 1805 when he was elected to the newly created chair of surgery in the University of Pennsylvania. Through the influence of John Hunter and others, surgery was becoming less an illegitimate child of medicine. Accordingly, on May 7, 1805, the medical faculty, belatedly wishing to meet the needs of their students, requested the Board of Trustees to dissolve the combined Professorship of Anatomy, Midwifery and Surgery and to establish a separate chair of surgery.[56] The abandonment of the combined chair, an Edinburgh institution, was one of the first indications that American medical education was developing an identity distinct from European schools. Carson states that the Chair of Surgery was "created by and for Doctor Physick".[57] However, a faculty which included Rush, his old enemy Kuhn, and Wistar, who Rush felt had betrayed him, could not escape some intrigue when a new appointment arose. Wistar, who was an Adjunct Professor of Anatomy, coveted the new position, but Rush successfully sponsored his rival, Physick. Physick's ultimate success certainly justified his appointment.

The two friends were conscientious faculty members and were always in agreement when an academic dispute arose. They, with other faculty members, petitioned the trustees in 1806 to delete the requirement for a medical thesis.[58] This European practice was eventually abandoned by the University of Pennsylvania and other American medical schools.

Physick supported Rush in his successful campaign to defeat an attempt to detach chemistry from the medical faculty in 1809.[59] Rush dominated the chair during his lifetime, but whether chemistry was to be regarded as a basic science or a clinical one was a question

[52] Ms., letter from Benjamin Rush to Henry W. Physick, Philadelphia, Jan. 24, 1799, Historical Society of Pennsylvania.

[53] Benjamin Rush, *op. cit.*, 4: 148.

[54] S. L. Mitchill and E. Miller, (Editors), *Medical Repository* New York, Vol. I, 1804, p. 102.

[55] Jacob Randolph, *op. cit.*, p. 56.

[56] Ms., Archives of the University of Pennsylvania, Vol. V, May 7, 1805.

[57] Joseph Carson, *History of the Medical Department of the University of Pennsylvania*, (Philadelphia, 1869), p. 104.

[58] Ms., Archives of University of Pennsylvania, Vol. V, May 22, 1806.

[59] Ms., Archives of the University of Pennsylvania, Vol. VI, July 6, 1809.

which flared up again after Rush's death and was not satisfactorily settled until many years later. Physick always held Rush's view that chemistry was a clinical science.[60]

Some of the medical faculty's problems are still encountered today. In 1810, the medical faculty had difficulty convincing the Board of Trustees that certain improvements were necessary. Physick and Rush played prominent roles in formulating a petition which asked for additional faculty members to accommodate increasing enrollments.[61]

Their academic association was sometimes of a more personal nature. Physick, whose health was always fragile, requested that his nephew, John Syng Dorsey, be appointed an adjunct Professor of surgery in 1807, to aid him. The faculty reluctantly approved his request, but recommended to the Trustees that Dorsey not be paid. The Trustees, however, appointed Dorsey with remuneration.[62] No documentation exists of Rush's point of view, but it is reasonable to assume that he used his influence with the Trustees, for as early as 1804, he had urged Dorsey "to come and help [his] uncle."[63] Dorsey became a popular professor and wrote the first American textbook of systematic surgery.

Another significant contribution was made in 1808 when Rush and Physick successfully petitioned the Pennsylvania Hospital to allow their senior students to perform the initial examination of patients seeking admission to the hospital with ultimate responsibility for treatment remaining with Doctors Rush and Physick.[64] This educational practice is used by medical schools today.

The improved medical education provided by the University of Pennsylvania and other American schools provided the young country with improved medical care. The arduous task of overtaking European medical standards, begun early in the nineteenth century was not accomplished until the twentieth century.

Rush was among the first American physicians to doubt the supremacy of European medicine. His son, studying in Edinburgh in 1810, informed him that Edinburgh physicians were not superior to Philadelphia doctors. This information pleased Rush, but he had no desire to start an international medical quarrel. He informed his son; "I have concealed the contents of your letters from everybody except Doctor Physick, and for reasons that must be obvious to you."[65]

Rush, however, was not reluctant to express his views to students. In 1811, he advised a student who was contemplating European study, "your notes of Doctor Physick's lectures probably contain more knowledge [of surgery] than you could acquire even under the most favorable circumstance in which you could visit [Europe] in the course of two or three years."[66]

Their association of twenty years ended with Rush's death in 1813. Mrs. Julia Rush described his last hours. He became ill on April 14, 1813, but at first prescribed for himself, i.e., he had himself bled. Dorsey, often called Physick's *alter ego*, visited Rush, made some recommendations, and left him apparently not too ill. Rush's condition worsened and Dorsey returned. Dorsey objected to Rush losing more blood and called in Physick who

[60] For an excellent discussion of this conflict see "A Short History of the Professorship of Chemistry of the University of Pennsylvania School of Medicine 1765–1847", by Herbert S. Klickstein in the *Bulletin of the History of Medicine*, Vol. 27, No. 1, Jan–Feb. 1953.

[61] Ms., Archives of the University of Pennsylvania, Vol. VI, Dec. 4, 1810.

[62] Ms., Archives of the University of Pennsylvania, Vol. V, Oct. 6, 1807.

[63] L. H. Butterfield, *op. cit.*, p. 882. Letter from Benjamin Rush to John Syng Dorsey, Philadelphia, May 23, 1804.

[64] Ms., letter from Benjamin Rush and Philip Syng Physick to the Board of Managers of the Pennsylvania Hospital, Nov. 28, 1808. Pennsylvania Hospital Archives.

[65] Butterfield, *op. cit.*, p. 1038, Letter from Benjamin Rush to James Rush, Philadelphia, March 19, 1810.

[66] L. H. Butterfield, *op. cit.*, p. 1097, Letter from Benjamin Rush to Jos. Bradner Stuart, Philadelphia, Aug. 24, 1811.

agreed. His breathing became more difficult and Physick consented to his losing three ounces of blood. He seemed to improve and Physick assured Mrs. Rush that he was getting well. The day before Rush's death Physick and Dorsey visited him and found that his condition had deteriorated. When they returned later in the day, they knew he had not long to live.[67] A relative of Physick's wife wrote of Rush's death on April 19, 1813:

> Yesterday Doctor Rush paid the debt of nature, after a short illness supposed to be something of the typhus kind. Doctor Physick who was much with him says he was calm, patient, and resigned never uttering a murmur . . .[68]

Ashhurst at the Centennial Celebration of the College of Physicians related the following sequel to Rush's death:

> The evening after Doctor Rush died—this incident I heard from the lips of Doctor Norris—Doctor Physick was sitting in an upper room of his house, in a solemn frame of mind, as we can well believe, thinking of the events of the day, and of the death of the great physician with whom he had not always been in harmony. Summoned to go downstairs by a loud ring at the door-bell, he was confronted in the hall-way by an unusually large negro, who abruptly asked him, "Do you want Doctor Rush?" "What do you mean?" said Doctor Physick involuntarily recoiling, "Doctor Rush is dead." "I will have him at the college for you at nine o'clock tomorrow morning for twenty dollars," replied his burly visitor. It is needless to say that this kind offer was not accepted.[69]

Perhaps as Middleton suggests this incident was the reason for Physick's dying request that a guard be placed over his grave to protect it from resurrectionists.

The story of Rush and Physick does not end with Rush's death and this anecdote. Rush's medical practice had been so damaged by his quarrels that his income had diminished. The economic boon which he received as a result of being appointed Treasurer of the U. S. Mint in 1799 by President Adams helped him support his large family. His estate, however, was modest. Rush had used his influence to further Physick's career. After Rush's death, Physick attempted to repay him. Physick was well acquainted with President and Mrs. Madison for he had lived with John Todd, Dolly Madison's father-in-law by her first marriage when he was a student, and when she sustained a knee injury in 1805, he treated her.[70] In 1813, Physick wrote to President James Madison:

> You are doubtless apprized of the death of my excellent friend Doctor Rush and I am sure you are sensible of the loss which society has thereby sustained. In consequence of the event I take the liberty of addressing you on a subject which I know to be very important to his bereaved family. If compatible with your own views the appointment of Dr. James Rush as successor to his father in the office of Treasurer to the Mint would . . . be extremely important especially as the absence of his elder brother places him at the head of a large family . . .
>
> I hope you will excuse the liberty I have taken in expressing a solicitude on this occasion as the long habits of intimate friendship which have existed between the late Doctor Rush and myself make it impossible for me to be indifferent to the interests of his widowed children.[71]

James Rush, however, did not receive the appointment.

Although Physick's affection for Rush was great, he had never cared for Rush's quarrels. After Rush's death, Physick resumed friendships which had been strained by his close association with Rush. When he contracted typhus in the winter of 1813–14, Physick asked Wistar and Kuhn, Rush's adversaries, to attend him. He recovered from typhus, but

[67] Maurice B. Gordon, *Aesculapius Comes to the Colonies*, Ventnor, N. J., 1949, p. 472, p. letter from Mrs. Rush to Doctor Mease.

[68] Ms., Letter from Samuel and Susan Emlen to William Dillwyn, April 13–23, 1813, Library Co. of Philadelphia, (Ridgeway Branch).

[69] W. S. Middleton, "Philip Syng Physick" in Annals of Medical History, Vol. I, ns., 1929, p. 582.

[70] Ms., Dolly Madison Papers, George B. Cutts Collection, Library of Congress.

[71] Ms., Letter from Philip Syng Physick to James Madison, Philadelphia, April 21, 1813. Library of Congress.

his health remained poor until his death in 1837.[72]

During his association with Rush, Physick became the leading American Surgeon of his day. Upon him was bestowed the sobriquet, "Father of American Surgery" during his own lifetime. He made many mechanical improvements in surgical instruments and independent of Monro II invented the stomach pump. He was the first American surgeon to use catgut sutures extensively. At the age of sixty-three, he successfully performed a lithotomy upon John Marshall when the Chief Justice was seventy-six years old.[73]

Physick's greatest influence was as a teacher. His *forte* was conservative surgery and through him, Hunter's methods and discoveries were taught to nineteenth century American physicians. As he published no *magnum opus*, student notebooks of his surgical lectures were carefully saved.[74]

Although Rush—his second great preceptor—interested Physick in some of his perhaps sounder notions, i.e., temperance and the abolition of slavery, his medical theories were less sound. While Physick's students heard of Hunter's experiments on blood and his work on gunshot wounds, he also told them:

> When called in an early stage of above symptoms [inflamed joint] the cure is not extremely difficult. I generally draw blood from arm [and] prescribe purge every other day to be continued six weeks or two months. The best purge for children . . . I have found should be given in doses sufficient to procure four or five stools a day. It is astonishing how patients bear these evacuations as well as they do.[75]

Twentieth century pediatricians would be even more astonished than Doctor Physick. Benjamin Rush, however, would have approved.

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[72] W. E. Horner, *Necrological Notice of Dr. Philip Syng Physick*, Philadelphia, 1838, p. 13.

[73] L. R. C. Agnew and G. F. Sheldon, "Philip Syng Physick (1768–1837): 'The Father of American Surgery' ", in the Journal of Medical Education, vol. 35, No. 6, pp. 541–549, June 1960.

[74] The author has located twenty-seven student notebooks of Physick's lectures.

[75] Ms., Lecture Notes on Surgery delivered by Philip Syng Physick, Professor in the Univ. of Pennsylvania, taken by Samuel Harris, Oct. 1809. Clendening Library, Kansas University Medical Center.

Memoir of Major-General Sir Robert McCarrison (1878–1960)*

By FRED B. ROGERS, M.D.

MAJOR-GENERAL Sir Robert McCarrison, Indian Medical Service, Retired, Kt., C.B.E., M.D., Sc.D., LL.D., F.R.C.P., and honorary Foreign Fellow of the College of Physicians of Philadelphia since 1922, died in Oxford, England, on May 18, 1960 at the age of 82. First Director of the Nutrition Research Laboratories at Coonoor, Southern India, his work pertained not only to India, but extended to medicine in general, including particularly significant studies on goiter, cretinism, and other deficiency diseases. His Mary Scott Newbold Lecture before this College, on November 11, 1921, was related to this field of interest; it was titled, "Some Effects of Faulty Food on the Endocrine Glands," (*Transactions*, XLIII, 473–494, 1921).

Robert McCarrison was born at Portadown, County Armagh, Northern Ireland, on March 15, 1878. He studied medicine at Queen's College, Belfast, graduating M.B., Ch.B., with honors, in 1900. He received his M.D. degree in 1909, the year in which he also became a Member of the Royal College of Physicians, London. He was elected F.R.C.P. in 1914, and received the degree of Sc.D. at Belfast in 1915.

McCarrison entered the Indian Medical Service soon after graduation in medicine and earned a reputation as a first-order research worker. The First World War interrupted his researches in India; he served at an Army General Hospital in Egypt and later was in charge of a Malaria Investigation Center. In 1918 he was made brevet lieutenant-colonel for distinguished medical service.

Returning to India in the same year, he began work at the Pasteur Institute, Coonoor, and remained there until his retirement in 1935, when he settled at Oxford, England. He served as president of the Section of Nutrition of the British Medical Association in 1937, and as chairman of its Oxford Division during the Second World War—also serving then as a group officer in the Emergency Medical Service. From 1945 to 1955, he was director of Postgraduate Medical Education at Oxford University.

Many honors came to him. He was appointed Commander of the British Empire in 1923 and knighted ten years later. In 1922 he was elected one of the twenty possible Honorary Fellows of the College of Physicians of Philadelphia—the first since 1909, a thirteen year period which included the First World War. (Dr. William J. Taylor, then president of the College, was a brother-in-law of the donor of the Newbold lectureship which McCarrison graced in 1921.)

In 1918 he received an honorary LL.D. degree from his *alma mater*, Queen's University, Belfast. From 1928 to 1935 he was Honorary Physician to the King. His Cantor Lectures to the Royal Society of Arts were published in book form with the title, *Nutrition and Health*; he received the silver medal of this body in 1925. The British Medical Association, in 1918, awarded him its Stewart Prize for studies in the epidemiology of infectious diseases. His major work, *Studies in Deficiency Diseases*, was published in 1921; this work is still referred to as a classic in its field. An earlier book, *The Thyroid Gland in Health and Disease*, was based on his Milroy lectures before the Royal College of Physicians in 1913—and research on endemic goiter which he continued in India until 1935.

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In 1922 he received the Arnott memorial gold medal of the Irish Medical Schools and Graduates Association, and in 1934 the Wagner-Jauregg Foundation Prize of Vienna—the first such award to a foreigner. His broad studies on diet and disease were based on combined field observations and investigations on laboratory animals. McCarrison's contributions to science were described in detail in a volume, *The Work of Sir Robert McCarrison* (edited by H. M. Sinclair), published in 1953 on the occasion of his 75th birthday. Dr. E. V. McCollum, another pioneer nutrition research worker, wrote of him in that volume:

"Sir Robert possesses in enviable measure qualities which are admirable in the eyes of his many friends and admirers. Intellectual honesty, enthusiasm, curiosity, studious attention to interpreting his observations in the full light of the work of others, courage of conviction in unusual measure in defending his considered conclusions are characteristic of him. He possesses not only knowledge but wisdom."

Described as an effective orator, he brought vitality to scientific subjects when he spoke and manifested an enduring love for India—the country where he spent so many productive years. In return, he received a measure of affection which India has given to relatively few Europeans.

He married Helen Stella Johnston in 1906; to his widow goes the sympathy and respect of this College upon the passing of a nobleman in medical science.

Memoir of William Stell Newcomet (1872–1960)*

By EUGENE P. PENDERGRASS, M.D., SC.D.

DR. WILLIAM S. NEWCOMET was born in Philadelphia on July 20, 1872, and died at his home, 3501 Baring Street, September 9, 1960, at the age of 88 years. The immediate cause of death was metastatic carcinoma. Eighteen months before, Dr. Newcomet had been operated upon for a carcinoma of the colon. He made a good recovery, but later was reoperated upon for intestinal obstruction and finally succumbed to extensive metastatic disease.

Dr. Newcomet's parents were of Pennsylvania-German stock and from them he inherited the characteristics so often observed in those of Pennsylvania Dutch ancestry—thrift and using one's time well. His kindliness of nature and his consideration of others endeared him to his friends, his colleagues and patients. One of his friends has written; "Were I to compile a list of those whom I found most unselfish, humanitarian and worth while, Dr. William S. Newcomet's name would be on top or near the top of the list."

His father, Henry Walborn Newcomet, was born in Berks County, Pennsylvania, received an A.B. degree from Franklin and Marshall College, and his M.D. degree from the University of Pennsylvania in 1865. His mother was Elizabeth Kesia Stell of Philadelphia.

William S. Newcomet received his primary education in Philadelphia. He attended Friends' Girard Avenue School and the Lauderbach Academy. At the age of thirteen, following his father's early death, his mother decided to take her three children to Europe. While there, William Newcomet enrolled at the University of Berlin (1888–1889) and remained for a period after his family returned home. His major interest was in chemistry. The instruction that he received in German and in chemistry were to be of great value in his medical career. In 1890, he returned to Philadelphia and matriculated at the Medical School of the University of Pennsylvania from which he received his M.D. degree in 1893. After serving a year of internship at St. Agnes Hospital in Philadelphia, Dr. Newcomet entered general practice. From 1894 he was associated with the St. Agnes Hospital, the medical clinic of the University of Pennsylvania, the Rush Hospital for Consumptives, the Women's Hospital, the Pennsylvania Hospital for Nervous and Mental Diseases, and was attending physician to the House of the Good Shepherd.

At the Rush Hospital in 1898, where he served as pathologist (2), Dr. Newcomet became interested in the employment of x-rays in the study of the chest. In 1899 he became the director of the x-ray department of the Presbyterian Hospital in Philadelphia, a position which he occupied for approximately fifty years.

The Oncologic Hospital of Pennsylvania was organized in 1904. Dr. Newcomet was placed in charge of the x-ray department and was a major influence in the development of cancer therapy in that great and somewhat unique institution. The Oncologic Hospital obtained its first radium in 1907. As the use of radon came into vogue, it became necessary to acquire a radon plant. As the trustees did not have the funds to purchase the unit, Dr. Newcomet successfully built a plant on his own initiative. This included machining the intricate parts of the unit and blowing his own glass tubes. The unit was completed in 1920 or 1921, and enabled the Oncologic Hospital to

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supply radon to many parts of the United States. Dr. Newcomet early became chairman of the medical staff; a position that he held for many years. Some time after Dr. Newcomet had completed the emanation plant, the Trustees, in appreciation of his tireless and unselfish devotion to the Hospital, with appropriate remarks, gave him a silver service.

Dr. Newcomet, as always, was self-effacing and accepted the gift on behalf of himself and his wife, who on that day were celebrating their twenty-fifth wedding anniversary. No one ever disillusioned him about the gift, and all were pledged to secrecy and I am told that Dr. Newcomet never suspected any other motive that the Trustees might have had.

Dr. Newcomet endeared himself to the Staff and Trustees on many occasions. In order to illustrate the facets to his character, I will relate another incident. In 1905, the Trustees rented an old dwelling house at 45th and Chestnut Streets, with an option to buy. Early in 1911, the agents threatened to more than double the rent and made the option to buy prohibitive because they felt that the Trustees had no alternative unless they exercised the option. To the agents' surprise the house and site were abandoned at midnight when their option expired. All patients had been moved without mishap to the present location which was acquired in 1911. Dr. Newcomet was largely responsible for seeing that all patients were removed to the present location without undue distress or discomfort. The old site and house were unoccupied for a decade or two thereafter. Thus Dr. Newcomet, a quiet and unaggressive person, for the first time showed his fighting spirit for the benefit of the Hospital.

Dr. Newcomet was Clinical Professor of Roentgenology at Temple University School of Medicine for three years (1912–1915). He resigned to take charge of the Radium Department at Jefferson Hospital. Dr. Newcomet constructed an emanation plant at Jefferson in 1916; this was the first one in Philadelphia.

It was during that period that several Philadelphia radiologists, physicists and electrical engineers were responsible for many of the developments in radiology. Some of these included Kassabian, Pfahler, Leonard, Newcomet, Pancoast and Snook. It is of real interest to document that in those early days it was recognized that x-rays and radium were known to be dangerous unless caution and protective devices were employed. In 1903, Dr. Newcomet wrote on "Carelessness in the Use of Roentgen Rays." He knew the dangers and observed them. So far as I know, Dr. Newcomet did not suffer from radiation damage to any part of his body. Some of his close friends, such as Doctors Kassabian, Leonard and Pfahler, were not so fortunate.

It would seem appropriate to state that the developments concerned with x-rays in Philadelphia attracted attention all over the world. Possibly one of the main factors was the organization of the Philadelphia Roentgen Ray Society by Doctors Leonard, Pfahler, Shober, Goodspeed, Pancoast, Snook, Newcomet and others in 1905. These pioneers used to meet in each other's offices at frequent intervals and discuss mutual problems. It was during this period that Dr. Pfahler and Dr. Newcomet popularized the use of x-ray filters, Mr. Clyde Snook developed the x-ray transformer, Dr. H. Threlkelv-Edwards developed his intensifying screens, Dr. William Sweet invented his foreign body eye localizer, and Dr. Newcomet pioneered the use of radium in treatment of cancer and other diseases. As a result of these inventions and explorations, it was realized very soon that Philadelphia should make an effort to provide postgraduate instruction in the new science. The Philadelphia Postgraduate School of Roentgenology, which was formed then, was the first of its kind in the United States and it remained in existence until 1915. The teachers included Doctors Newcomet, Pfahler, Manges, Bowen, Pancoast, and Mr. Snook. Instruction was given in the following hospitals: Philadelphia General, Jefferson, Presbyterian, Oncologic, Pennsylvania (8th & Spruce Sts.), Medico-Chirurgical, and the University of Pennsyl-

vania. The course was given to six graduate physicians. The instruction consisted of demonstrations of patients, technic, and discussions of practical clinical problems for a period of one month. The class was kept busy all day and the fee was $150.00 payable in advance. The course was a success and it is said that it was a forerunner of the Graduate School of Medicine of the University of Pennsylvania (1). The esprit de corps among radiologists that prevailed in Philadelphia in those early days is a heritage of which we are proud and it can be said that it still obtains.

In 1916, Dr. Newcomet joined the Red Cross unit of the Presbyterian Hospital and entered the Army as a 1st Lieutenant, June 15, 1917. He served at Camp Greenleaf and Camp Gordon in Georgia as Acting Adjutant in charge of the x-ray department, Instructor in the rules of the Army Survey and Court Officer from June 1917 to 1919. At General Hospital, No. 35, West Baden, Indiana, he was in charge of the x-ray department from February 1919 to April 29, 1919, when he retired as a Major. He was advanced to a Lieutenant Colonel in the Reserve Corps in 1920.

Dr. Newcomet was not a joiner but was interested in organized medicine and was a very active participant in many organizations:

- The Philadelphia County Medical Society, Vice President and member of the Board of Directors for 11 years
- The Pathological Society of Philadelphia (1894–)
- Fellow of the College of Physicians of Philadelphia since 1905
- President, West Branch Philadelphia County Society, 1917
- Fellow, American Medical Association
- Fourth Vice President, American Roentgen Ray Society, 1909
- Secretary, American Radium Society, and President in 1924
- Fellow of the College of Radiology
- Diplomate of the American Board of Radiology
- Member of the Franklin Institute (1944–1960)
- Member of the American and Philadelphia Mineralogical Societies
- Active and devoted Mason and Past Master in the Stephen Girard Lodge #450, Pennsylvania.

In 1907, Dr. Newcomet established a trust fund of $1,000 (now administered by the College), the income of which was to be used for the purchase of books for the library in memory of his mother, Elizabeth K. Newcomet. The income from this fund to purchase books has been used continuously since 1908. Dr. Newcomet's books have been given to the library by his daughter, Mrs. Paul W. Sutro.

Dr. Newcomet was well known to earlier and present generations of radiologists, even though he had been retired and inactive for a number of years. A testimonial dinner in his honor was given by the Philadelphia Roentgen Ray Society on June 12, 1942. The Annual Oration in honor of William S. Newcomet, pioneer radiologist and charter member of the Philadelphia Roentgen Ray Society, was delivered by Dr. Bernard P. Widmann on November 6, 1958. "Uncle Bill," as I called him, was a quiet and gentle physician with a good sense of humor and was liked by everyone. His ideals were on a high plane. His knowledge of physics and chemistry provided the background for much of his early work in radium and roentgen therapy. He was well informed on the world's literature and generously contributed to it—some 59 original articles and a monograph.

His publications indicate a wide field of interest. His observations on chest diseases date back to 1899. His publications on the "Treatment of Malignant Disease with x-rays" in 1903; "Pathological Changes in Tissue under the influence of the x-rays" and his book, "Radium and Radiotherapy" published by Lea and Febiger in 1914, have stood the test of time, and many of the observations are in accord with current thinking. Dr. Newcomet's greatest interest probably was in therapy, especially with the use of radium, and he developed a well earned reputation in the care of hemangiomas in children.

Dr. Newcomet's chief interest was his profession. He rarely took vacations, but he did travel around medical clinics in Europe when time and money were available (2). He had several hobbies from which he derived great enjoyment. One of these was automobiles (2).

Dr. and Mrs. Newcomet spent many happy hours along the Brandywine while he sketched that lovely Pennsylvania stream. From childhood he was an avid collector of minerals and as he grew older he made trips to many mines and caves to obtain new specimens for his large collection. He was particularly interested in fluorescent minerals and fond of showing them under various lights. His hobby of keeping bees on occasion presented problems in his city home when they would swarm and leave for greener pastures.

On April 22, 1897, Dr. Newcomet married Katherine E. Mackeown. His daughter, Mrs. Paul W. Sutro and three grandchildren survive him.

In a report (1913) to his classmates (2), Dr. Newcomet said: "My success is measured by a story told by my daughter, which was overheard by her mother. At a hotel some years ago, several children were quizzing her as to her station in society. One asked, "Is your father rich?" She replied, "No." "Is he poor?" Answer, "No" "Then what is he?" The youngster replied, "Well, he's just comfortable." So that is my answer to the question as to success, I'm just comfortable."

Thus I come to the end of this memoir of a quiet dignified physician and scientist. Death ended the career of a man whose life had been one of achievement and enrichment for himself, for medicine, and for those who were privileged to know him. As time passes, many will arise to fill his place in the vineyards of medicine and science wherein he labored, but in the final estimation, any man who can properly be classified with William S. Newcomet shall be happy indeed.

(The author is indebted to Mrs. Paul W. Sutro, Dr. W. B. McDaniel, 2d, Dr. George E. Nitzsche, Dr. W. F. G. Swann, Dr. Richard A. Kern, Dr. Bernard P. Widmann, Miss Frances Houston, Mr. H. Kenneth Hodges, Dr. John T. Farrell, Dr. William A. Sodeman, and Mr. William F. Jackson, Jr., for their help in collecting data about Dr. Newcomet, most of which was used in the preparation of this memoir.)

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Memoir of Maurice S. Jacobs (1897–1960)*

By SAMUEL X RADBILL, M.D.

"HONOR a physician according to thy need of him with the honors due unto him." Thus spoke Koheleth, "The Preacher, the Son of David, King of Jerusalem."

It is fitting that we should thus honor our departed colleagues with the traditional memoirs of the College of Physicians of Philadelphia.

Maurice Spencer Jacobs was born in Liverpool, England, July 23rd, 1897. There he attended the Jewish Parochial School. The teacher of the Talmud-Torah, by dint of constant repetition, aloud and in unison, drummed into his infant students the words of the prophets and the sages, leaving an indelible impression upon the mind and the personality. At home, parental praise and adulation were then heaped upon the impressionable child who proved to be an adept scholar. Thus, at an early age, the love of The Book, of learning, was inculcated in the children of Israel.

At the age of seven, Maurice moved with his family to Philadelphia. Here he continued his education in the elementary public schools and graduated in 1916 from the South Philadelphia High School in the days when a full academic schedule was prescribed for the student. Frivolous time was not spent on "electives" and we never heard of "study periods." The roster was a full one with every hour of the school day fully occupied.

He then went to the University of Pennsylvania, received his A.B. in due course, and graduated from the School of Medicine in 1923. After attaining his M.D., in conformity with the requirement for medical licensure in this state, he served for one year as an interne at the Jewish Hospital of Philadelphia. With this Institution (which will soon celebrate its hundredth anniversary) he was thereafter associated throughout his entire professional career.

Following internship, Dr. Jacobs opened an office in West Oak Lane, to practice "medicine and surgery" as specified by the license to practice in Pennsylvania. Here he was in general practice for about seven years. During this period he interested himself particularly in pulmonary diseases, no doubt influenced by his friend, Dr. Burgess L. Gordon, with whom he became associated. He joined the staff of the Department for Diseases of the Chest at the Jefferson Hospital about 1927 and was active there for more than a decade. He was also attached to the Division of Tuberculosis in the Philadelphia Department of Health. He perfected himself in the technique of artificial pneumothorax, a form of treatment that had its hey day for several decades before chemotherapy took the ascendancy, and also became adept in perinasal lipiodol installations following the precepts of Jacques Forrestier. Much of this work he carried out at the Rush Hospital of Philadelphia.

The year 1930 was an important turning point in his life. He married Minnie Blume, was elected a Fellow of the College of Physicians of Philadelphia, and, moved by the prevailing trend, determined to specialize in cardiology, then a burgeoning field of medical practice. He chose Vienna for his post-graduate studies. There he worked under Dr. Hugo Roesler, who came to Philadelphia soon afterward to join the medical teaching staff at Temple University.

Upon his return to Pihladelphia, Dr. Jacobs opened a town office in conjunction with Dr.

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Nathan Blumberg, and limited his practice to cardiovascular diseases. Along with Dr. Joseph Sailer, he was among the first to use the electrocardiograph in its present form in clinical work. When the Jewish Hospital affiliated with Temple University, he joined the teaching faculty on the staff of Dr. Joseph C. Doane. As Dr. Blumberg relates, he always had an inquisitive mind, a good brain and was a good teacher.

In 1941 he became a Diplomate of the American Board of Internal Medicine when that certifying body was still in its infancy; soon after, he was elected a Fellow of the American College of Physicians.

In 1916, at the age of 19, he graduated from Gratz College, a school which had been established in 1895 by the Mikveh Israel Congregation of Philadelphia, through the benevolence of one of our city's leading Jewish citizens, for the education of Jews residing in this city and country. The enthusiasm of Dr. Jacobs for Hebrew Philosophy and Judaic Lore was unbounded and lasted throughout his life. He organized adult educational classes in Hebrew, in Jewish History, in Biblical and Talmudic Studies, and when, because of failing health, he retired from active practice, in 1955, he took graduate courses at the Dropsie College of Hebrew and Cognate Learning in Philadelphia. Truly a "Seeker of Knowledge," he was president of Dorshe Da' Ath, a group in which each member is required to prepare a paper in succession upon some phase of Jewish culture. He was also president of the Hebrew Culture Society, an organization similarly consecrated to the study of Hebrew Culture. An avid supporter of the young State of Israel, he visited that country in 1950 and again in 1954, lectured there, and in the summer of 1959, sent 1200 volumes from his own library to help form the nucleus of a new medical library in Jerusalem.

His interest in medical history was aroused when he was fresh out of medical school. Dr. Gordon recalls his first excursions into history when he grew curious about the buildings in the neighborhood of 238 Pine Street, their background and uses during the rise and fall of this historic area. He gave a most interesting talk on the subject at one of the staff meetings. As a Fellow of the College of Physicians he took an active part in the affairs of the Section on Medical History, serving as Clerk, chairman and section committee member, and frequently appearing on the programs. During the earlier years of his Fellowship, he served also in these offices of the Section on Public Health, Preventive and Industrial Medicine.

For many years he was a member of the Northern Medical Association of Philadelphia, elected president, developed its history and wrote its story for the hundredth anniversary celebration in 1946. During his general practice days he found time to write scientific papers on the Treatment of Pulmonary Infections, and on Pneumohemopericardium; these were followed later by papers on the Heart in Uterine Myoma, Coronary Artery Disease and Pulmonary Syphilis. At the Centennial Celebration of the Philadelphia County Medical Society we find him in a "Two Act Dramatic Sketch" by that "playwright," our own Honorary Fellow, Richard H. Shryock. This playlet, entitled "One Hundred Years of Medicine" starred Maurice S. Jacobs as the antiquated "Dr. Baily" practicing in 1849, contrasting with the superscientific modern doctor of 1949 in the person of Dr. Richard A. Kern.

Among his historical papers were articles on "Maimonides, a Modern Physician", "The History of Digitalis Therapy," "Preventive Medicine in the Bible and Talmud," and "Circumcision." At the meetings of the American Association for the History of Medicine he was a steady participant, presenting papers on "Paul Ehrlich," "Thomas Beddoes and His Contribution to the Treatment of Tuberculosis," "Philadelphia in 1846: Men and Events that Influenced the Development of Organized Medicine," and "The Place of History in Medical Education." At the International Association for the History of Medicine meeting in Rome, Italy, he presented to a large audience, gathered

from the four corners of the earth and including Soviet colleagues at a time when their presence was indeed an exciting novelty, a paper on an esteemed former Fellow of this College in whose honor this meeting hall is named: "S. Weir Mitchell." Pointing out the European influence on Weir Mitchell's training, his work in the field of neurology and his love for the humanities, among other relevant anecdotes, he told about the head of an ancient Roman soldier which Dr. Mitchell kept in a glass case in his office. Dr. Jacobs then ended his paper with Dr. Mitchell's poem on the old Roman: "Guidarello Guidarelli."

"Mauri" Jacobs was a vocational practitioner. In spite of his diversity of interests, he sincerely believed that first and foremost was his responsibility to his patients. The long and difficult years of training for medical practice, he felt should be put to practical use. As a result he had a very large following in cardiology. But the arduous work of the practitioner does not preclude scholarship. This is well illustrated in the life of Dr. Jacobs. As a result of his many activities he was revered by his patients, respected by many friends in the field of Hebrew studies and acknowledged by his professional brothers for his contributions to medical history.

His death on October 9, 1960 has left us with a good name.

"A good name is better than precious ointment; and the day of death than the day of one's birth."

Memoir of John Oscar Bower (1885–1960)*

By HAROLD F. ROBERTSON, M.D.

DR. JOHN O. BOWER died of a cerebral hemorrhage on October 3rd, 1960. He was born in Newville, Pennsylvania on June 6th, 1885, the son of Adam and Rebecca Lay Bower. Dr. Bower graduated from the Carlisle High School in Carlisle, Pennsylvania, after which he attended and graduated from the Medico-Chirurgical School of Pharmacy at Philadelphia in 1905. He aspired to become a physician and in order to finance his way through medical school he owned and operated a pharmacy at Wyncote, Pennsylvania. He graduated as Doctor of Medicine from the Medico-Chirurgical College in 1909, and interned at the Temple University Hospital (formerly the Samaritan Hospital) from 1909 to 1910.

Dr. Bower subsequently became Clinical Professor of Surgery at the Temple University School of Medicine. He was also Chief in the Department of Surgery at Philadelphia General Hospital and Chief, Department of Surgery at St. Luke's and Children's Medical Center in Philadelphia. He was a member of the founder's group of the American Board of Surgery, and was certified as a specialist in 1938. He was Chairman of the Pennsylvania State Commission for Acute Appendicitis Mortality and was responsible for the widespread public educational campaign on laxative-induced peritonitis complicating acute appendicitis. Dr. Bower organized and headed The Foundation for Clinical and Surgical Research at Wyncote, Pennsylvania. In conjunction with this Foundation, he was the author of many papers on acute appendicitis mortality, research on the prevention of irreversible shock and spreading peritonitis, spinal anaesthesia, the superiority of catgut sutures, surgical nursing care, and many other surgical research problems. He was a member of the Society of the Sigma Xi, University of Pennsylvania Chapter.

He served as Captain in the Army Medical Corps during World War I, and was a member of the Medical Advisory Board for Selective Service in World War II. He was a Fellow of the College of Physicians of Philadelphia (elected 1923), and of the American College of Surgeons, a member of the American Medical Association, the Pennsylvania State Medical Society, and the Philadelphia County Medical Society.

Surviving Dr. Bower are his wife, the former Armorel Dixson whom he married in Payton, Utah, in 1918; three daughters and three sons; one brother, three sisters, and seven grandchildren.

Those who knew John O. Bower fondly recall his dedication to Christianity as a good churchman, his integrity and sincerity with colleagues and patients, his constant devotion to ill physicians and their families, and his profound concern and deeply conscientious efforts in behalf of all who sought his expert guidance. His passing is a great loss to the medical profession.

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Liver Circulation, Liver Function, and Liver Integrity[1]

By RALPH W. BRAUER, PH.D.[2]

THERE are two kinds of lecture which to me have always appeared to be especially enjoyable: One starts with words to the general effect: "I just happen to have one or two slides in my pocket to illustrate . . .", launching the speaker forth into a more or less spontaneous presentation of facts and ideas as the basis for further discussion. The other kind of talk is anything but spontaneous, but rather involves an attempt to translate a package of observations and hypothesis which have been accumulating for some time in the speaker's mind into a story that might make them meaningful and useful to the scientific community at large. I take it that the Mary Scott Newbold Lecture before this august body represents an instance of this second kind of presentation. Thus, not only do I feel deeply honored to have been invited to follow the long list of distinguished speakers who before me have occupied this lectureship. I am also very sincerely grateful to your lecture committee for giving me this opportunity to present to you, as it were, a "state of our work" message summing up a good many of the things which my colleagues and I have been thinking about for some time.

Physiology as a branch of the biological sciences has avowed its concern with the function of organs or organ systems, and more recently it has come to accept the desire for quantitative description as an essential part of the definition of its sphere of endeavor. These aspirations are fairly readily met in the case of structures the major role of which it is to produce mechanical or electrical effects which can be measured and expressed as work. Muscle and nerve have forever been favorite subjects of physiological study, and with the penetration of some of the concepts of hydrodynamics into this area of biology, the heart and the circulation, too, have come to be accepted. When one turns from such subjects, however, to tissues or organs which don't twitch, don't produce electrical impulses to any important degree, and don't move fluids at such a rate that their kinetic energy accounts for any important part of the energy balance of the tissue, the concept of function has proved far less amenable to physiological analysis: The kidney, for instance, did not join the select circle of popular study subjects until the thoughtful and ingenious work of scientists like A. N. Richards and Homer Smith had provided a conceptual framework

[1] Mary Scott Newbold Lecture LXXXI, 1 February 1961.

[2] Head, Pharmacology Branch, U. S. Naval Radiological Defense Laboratory, San Francisco 24, California.

within which a rigid analysis of renal function, both in terms of anatomical units and in terms of the body's fluid and electrolyte household, could be attempted.

It is in this same general category that we must place the liver: Its one visible performance, the secretion of bile, involves only slowly moving fluid of such composition that the work of secretion here clearly is in the somewhat subtle form of chemical rather than hydrodynamic work; for the rest we are saddled with a plethora of functions (depending on your taste, you can enumerate 100, or 1000, or 5000), but a lack of anything readily defined as Liver Function and amenable to quantification. In recent years, one can begin to pick out here and there parameters which can be quantified and which gradually allow one to recognize the conceptual outlines of what with tender nursing might grow up to become a useable set of ideas to form the basis of a meaningful analysis of liver function. Prominent among these several presently approachable aspects of liver physiology is the fact that all quantifiable liver function measurement must presume an understanding and a quantitative description of the circulatory status of the liver. This is a direct result of the fact that, with the partial exception of bile secretion, all liver function involves the transfer of material between the hepatic parenchyma and the blood, or perhaps the lymph streams, and that the blood composition changes sustained in passage through the liver, the total amounts of materials transferred, and indeed the very mass of the liver itself, all are dependent to some extent upon the circulatory status of the organ. How important these circulatory determinants of liver function are in each particular case, and what role they might play in the regulation of liver function, cannot, assuredly, be determined *a priori* but must be derived from a careful analysis of the functional relationships (in the mathematicians' sense) for each case, or each category.

The outstanding feature of the hepatic vascular bed is the extraordinary degree of branching associated with the transition from the precapillary to the capillary—or rather the sinusoidal—portions of this circulation. This involves a high degree of ramification not only at the level of terminal distributing twigs, but at many levels, so that quite large portal branches may give off short twigs which directly enter the sinusoidal bed. The overall effect is to enmesh the parenchymal cells in an almost continuous fluid phase within which blood flow patterns can vary readily and widely in response to external forces affecting either the shape of the liver, the pressure within the tissue, or the pressure gradients within the vascular tree. A closer look at the anatomy of the hepatic vascular tree, while revealing an enormously complicated mass of detail, allows one to construct a rather simple scheme which seems to provide for just about all of the observed phenomena. Such a scheme includes a portal supply, entering directly into the sinusoidal bed; a hepatic arterial supply which may either empty into the portal channels at a level where these are still fairly large, or which may supply a capillary plexus enmeshing the small bile ducts and drain thence into the portal stream for the most part, or directly into the sinusoidal bed to a smaller (if any) degree; and a rather highly ramified hepatic venous drainage consisting of relatively large, lightly scaffolded vessels. (Biliary and lymphatic channels must be omitted for brevity's sake in this discussion.)

In the sinusoidal bed, I think it is well to recognize a distinction between those sinusoids which at any given time follow more or less the streamlines of the blood flow (one can visualize these in a three dimensional fluid phase containing a lattice of equivalent sources and sinks) and those which are more or less at right angles to the flow and pressure gradient patterns. These latter, which I like to refer to as the "ladder-rung sinusoids," obviously function under somewhat precarious hemodynamic conditions and are the ones responsible for a good deal of the reported intermittency of flow in the hepatic sinusoidal

bed. Within this relatively simple framework, it is possible to recognize a considerable number—at least a dozen—of possible patterns of variation which provide the degrees of freedom for any regulation of liver function by way of the liver circulation. Blood composition (local or general), blood flow distribution and total blood flow rate are the basic parameters in any description of the circulatory status of the liver.

It is my contention that the pressures under which blood moves in the greatest part of the hepatic vascular tree are such that most of the patterns of variation of the hepatic circulation can be brought about passively under the action of the physical forces acting upon the liver or within the liver, and that active vasomotion needs to be invoked only to bring about a very few, easily recognizable blood flow patterns. Thus, I would be inclined to give priority to a search for methods of demonstrating the occurrence of the various blood flow patterns within the liver, and for a clearer understanding of their functional consequences, in preference to elaborate attempts to discover and analyse possible modes of active vasomotor control within the liver. The crucial point in such an argument is clearly the measurement of the blood pressures in and around the hepatic vascular tree.

Disregarding for the moment the effects of intraabdominal pressure upon the portal pressure, both portal pressure and hepatic arterial pressures are fairly readily determined, yielding rather uniformly values around 12 to 15 cm of water relative to the hepatic hilum for the portal venous pressure in resting animals, and hepatic artery pressure equal to the prevailing peripheral arterial pressure of perhaps 140.0 to 170.0 cm of water. The hepatic venous pressure being low and not as readily accessible to measurement has been a bit more controversial, but those specifically concerned with this measurement, having taken the necessary precautions against the effects of partial obstruction of the hepatic venous stream, pretty well concur that its value is low, and close to mean values in the thoracic vena cava inferior. When we became interested in the subject, the first surprise we experienced was to find in the rabbit as well as in the rat, that a considerable pressure gradient exists in the inferior vena cava between points just below the liver and points just above the diaphragm, as pressure drop of 3 to 5 cm H_2O over a stretch of a couple of cm of seemingly large diameter blood vessel. The explanation for this phenomenon is found in the flexure of the vena cava in this region which results in a nearly kinked vessel with grossly restricted lumen where blood flow can be shown by cinéangiograms to assume a jet like character (1). To gain further insight into the pressure gradients that affect hepatic blood flow patterns, it became necessary to extend one's measurements to vessels which should be as close to the sinusoids as at all possible. This became feasible when a vastly improved method of liver transillumination was developed by Dr. K. Nakata (2), allowing prolonged observations of undamaged liver under conditions which permitted the introduction of micromanipulator guided micro needles. So far, we have been able to place these into the terminal portal twigs at the level of their breaking up into sinusoids, and into central venules; we have not yet achieved micropunctures of the sinusoids proper (3). Pressure measurements under these conditions can be made quite readily using the balanced dye injection methods developed long ago by Krogh and Landis and others. The principal results of these studies can be summarized in a path-pressure diagram (Figure 1). Of immediate significance to the present discussion, are the marked pressure drop within the portal tree prior to the sinusoids, and the very low pressures within the hepatic venules. As regards the former, this may provide the hemodynamic basis we have long missed to account for the gross shift in blood flow distribution described years ago by Daniel and Pritchard under the terms of "hilar" or "restricted" vs. "diffuse" states of the hepatic circulation (4). These data suggest that the portal venous tree normally displays

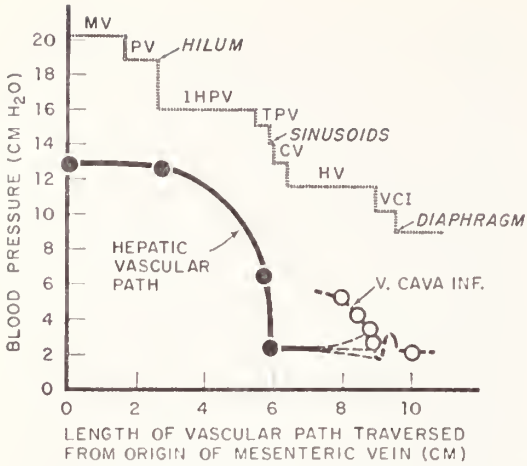

FIG. 1. Changes in blood pressure along the path of blood through the hepatic vascular tree (segments indicated are: MV—mesenteric vein, PV—portal vein, TPV—terminal portal venules, CV—central vein, HV—hepatic vein, VCI—vena cava inferior) (from (3)).

considerable resistance to blood flow, and that it may well be a major site of vasomotor regulation within the liver. This is borne out by studies with epinephrine which indicate that the resistance across the vascular segment between mesenteric veins and terminal portal twigs is indeed markedly increased under the action of this pressor amine (5). The second point of interest is that the hepatic venule pressures are so low that they yield a paradoxical pressure gradient relative to the site within the inferior vena cava where the hepatic veins drain. One might conjecture that these, after all, are only mean pressure measurements, and that there might be cyclic pressure fluctuations which restore a pressure gradient allowing the liver to drain. This in turn would imply an intermittent hepatic vein flow.

This conclusion could be put to the test directly by means of angiographic techniques Mr. McElroy and I were developing about a year ago (6). These allow nice visualization of hepatic vein flow in a number of species, and have confirmed the fact that hepatic vein flow is indeed intermittent, not only in the rat and the rabbit, but also in the dog and the cat. An additional fact of considerable interest brought out in the course of these studies was that in animals with an intact circulation the hepatic venous flow is synchronized with the respiratory cycle in such fashion that blood flow is maximal when the diaphragm is near its expiratory peak, i.e., at a time when the liver is under least amount of pressure, and when intrathoracic pressures are surely not minimal. Thus, evidently, neither the concept that the liver might be "squeezed out" like a sponge by the diaphragm, nor the concept that the intrathoracic pressure fluctuations passively determine hepatic venous flow can be accepted. As far as the former is concerned, while it is definitely not applicable to the normal liver, it may prove applicable to the congested organ: here a number of film sequences show that outflow is maximal during the descent of the diaphragm. As far as the normal liver is concerned, while we do not yet possess sufficiently detailed data concerning cyclic changes in pressure and flow within the diaphragmatic segment of the vena cava to complete this part of the analysis, we do have data on the part of the mechanism which may be responsible for stopping the hepatic venous flow.

In the course of a series of studies on the hemodynamics of the isolated perfused rat liver, Dr. Leong, Mr. Holloway and I had occasion to apply graded uniform pressures to the surface of the organ. The effect of this upon the flow pressure diagram is a quite drastic increase in perfusion resistance, associated with evidence of some decrease in the number of perfused channels, and a smaller decrease in the tissue blood volume (Figure 2). Recalling the collapsible, lightly scaffolded nature of the sinusoidal bed and of the hepatic venous tree, such collapse of vessels is surely not unexpected. An analysis of the sort of thing that should happen in a perfused nonrigid vessel subjected to uniform external pressure was performed years ago and showed that collapse of the vessels—*ceteris paribus*—should begin at the downstream end and progress upstream, squeezing the blood back

against the direction of normal flow (7); we do in fact have angiograms showing this very phenomenon under conditions where the diaphragm of rats was forcibly depressed by raising intrapulmonary pressures. Thus, the contracting diaphragm, by pressing upon the liver, tend to collapse part of the hepatic vessels furthest downstream, interrupting the flow of blood until the pressure has been released, and in this manner contributes to the cyclic intermittency of hepatic vein outflow. Suspension of respiration, as in a curarized animal on diffusion respiration (oxygen insufflation) eliminates intermittency of hepatic vein outflow in the rat, and does so apparently without changing the pressures we measure in the central veins of the liver margin (3). We have not yet checked the effect of this procedure upon the vena cava beyond establishing that it reduces the kink in the hepatic and diaphragmatic section of this vessel. This should decrease the pressure gradients across this segment and, judging by other reports, may well result in lowering the pressures against which the hepatic veins must discharge.

This series of observations, by calling attention to the increased hepatic resistance which results when the pressure upon the liver surface is raised even slightly, may also help in understanding the manner in which the hepatic parenchyma seems able to mold itself to the contours of the surrounding body wall and viscera. There is no reason to assume that the increased hepatic resistance—which we interpret under these conditions as reflecting passive changes in the hepatic parenchyma—can be elicited solely when the whole of the liver is brought under pressure. Indeed, transillumination observations long ago have shown that even quite localized surface pressure leads to a change in microcirculation patterns which clearly express the fact that flow through the region under pressure is more difficult than flow through immediately adjacent regions (8). Coupled with the high degree of branching of the portal tree, and the almost continuous character of the fluid

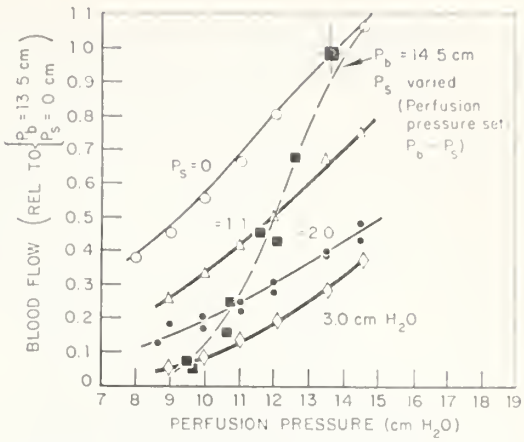

FIG. 2. The effect of pressure exerted upon the entire surface of the isolated perfused rat liver—upon the Flow Pressure Diagram. (P_b—portal pressure, P_s—surface pressure. The dashed curve represents the relation of blood flow to a calculated "effective perfusion pressure" equated to the difference between a fixed portal pressure and a variable surface pressure, and demonstrates that the effect of surface pressure is a far greater enhancement of hepatic resistance than any brought about by changes in portal pressure).

phase within the sinusoidal bed, these observations point to a high order of plasticity for blood flow patterns within the hepatic parenchyma, and a situation where the effect of sustained pressure upon any part of the liver surface should be the sustained reduction of blood flow through the portion of the parenchyma involved. On the other hand, ever since the classical experiments of Rous and Larimore (9), evidence has been accumulating to indicate that reduction of blood flow through any part of the liver entails the gradual atrophy of that part, with compensatory hypertrophy elsewhere if total hepatic blood flow remains constant. Coupled with what has just been developed concerning the effect of surface pressure upon tissue perfusion, these properties of the hepatic parenchyma are precisely the ones required to mold the liver to conform with the contours of its more resistant surroundings; the corset liver as well as a variety of post natal changes in liver shape in man; or even more nicely in the horse, are situations where one can observe these forces at work.

TABLE 1

DEGREE OF UNIFORMITY OF BLOOD FLOW DISTRIBUTION AND CELL POPULATION IN RAT LIVER

Lobe	Distribution of Tracer Doses of				Cell Population Data			
	$CrP^{32}O_4$ coll.		$BS^{35}P$		Parenchymal cells × $10^3/mm^3$		Kupffer cell / Parenchymal cell	
	Core	Margin / Core	Core	Margin / Core	Core	Margin / Core	Core	Margin / Core
LL	1.00	1.14	1.00	0.99	136	0.77	0.46	1.14
M	0.99	1.12	0.94	0.96	134	1.00		
RL	0.92	1.19	1.00	0.94	(147)	(0.77)		
C	0.99		1.06		140			
H	(0.84)				(116)			

( ) = single determination; remainder 4 animals per point.

One corollary of this analysis is that, as long as the parenchyma is healthy and basically uniform in its properties, the liver mass ought to be so adjusted to its blood supply as to display uniform tissue perfusion in all its parts not as a remarkable anatomical fact, but rather as the necessary outcome of the interplay of hemodynamics with the structure of the hepatic vascular tree, in the presence of the latent growth potential of the hepatic parenchyma. Dr. Krebs and I have recently put this hypothesis to a direct test by measuring the early distribution of two test substances throughout the several lobes of the liver, and between the margins and the hilar, or core, portion of the three major lobes of the rat liver (Table 1). There were no systematic differences in the distribution of S 35 sulfobromophthalein between the different parts; with chromic phosphate colloid we found a highly reproducible but small differential in such fashion that the liver margins contain about 15% more colloid per unit tissue weight than the core portions of the corresponding lobes. The histologic data incline us to interpret this latter fact as evidence of a slightly higher proportion of blood vessel surface per unit volume of parenchyma in the liver margin, possibly a consequence of the fact that parenchymal cells and littoral cells do not behave in quite the same fashion in liver tissue undergoing atrophy or hypertrophy (cf. results on $CrPO_4$ colloid uptake in the perfused regenerating rat liver). The overall conclusion, however, seems to bear out the prediction made above that mean tissue perfusion throughout the liver is indeed remarkably uniform. Indeed, in two animals we were fortunate in encountering sizeable herniated portions of the liver extending through the diaphragm into the thoracic cavity; even here the tissue perfusion was only slightly below the averages for the remainder of the corresponding livers.

These few examples must suffice to give you some impression of the kind of variability to be looked for in the hepatic circulation, and of the kind of interplay between the anatomy and the blood supply of the hepatic parenchyma. We must turn our attention now to the question of the role of the hepatic circulation in the control and in the measurement of liver function. To begin with, let me mention and perhaps define a few terms I shall be using off and on in the remainder of this presentation because of their convenience in describing some of the phenomena we shall have to discuss. In the first place, we shall have to talk about *hepatic clearance.* This is the product of the total amount of blood flowing through the liver in unit time, times the fraction of a given test substance removed from the blood stream in a single passage through the liver. This fraction, incidentally, I shall term the *extraction fraction* for brevity, and we shall have more to say about it pres-

ently. Meanwhile, you will have realized that the hepatic clearance is exactly analogous to the renal clearance, and that it can be thought of as the volume of blood completely cleared of the test substance in unit time. Its importance springs largely from the fact that when one considers the sort of steady state relations which underlie any kind of homeostatic regulation, it is the hepatic clearance and its relation to blood concentrations which determines the hepatic end of the regulatory mechanism. *Liver mass*, as I shall use it, is just what the term implies, the total mass of functional hepatic parenchyma available. We already know that there are conditions where not all of this parenchyma is supplied with actively flowing blood; I shall speak of the *perfusion fraction* to refer to the fraction of all possible vascular channels which are actively perfused at any given instant. Clearly the product of liver mass times perfusion fraction gives us an estimate of the magnitude of the *functioning liver mass*, and I shall so use this term. Finally, I shall distinguish *total hepatic blood flow* from the *tissue perfusion*, which I shall define as the volume of blood flowing through unit liver mass in unit time. This will be useful in particular in discussing those situations where the liver mass is a variable in our considerations. Thus, for instance, in partial hepatectomy experiments where the total hepatic blood flow is likely to remain relatively constant, the tissue perfusion will vary as the reciprocal of the liver mass left in place.

What happens to the hepatic clearance of some convenient test substances when we change the hepatic blood flow? The simplest situation perhaps is encountered in the case of those substances (and at those dose levels) where the extraction fraction is independent of the blood level. These conditions are generally met when the semilog plot of blood concentration against time after a single injection yields a straight line. The slope of such a line is a function of blood volume, hepatic blood flow, and the extraction fraction. Examination of a typical example

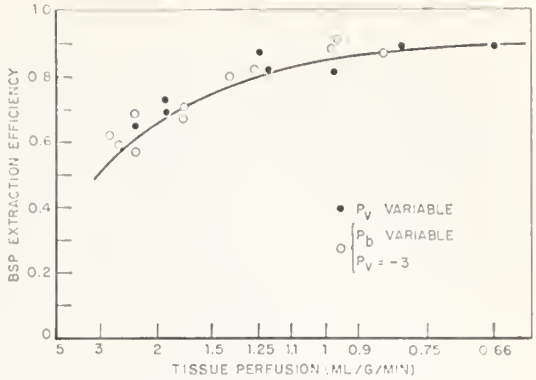

FIG. 3. Variation of extraction fraction for tracer doses of S^{35} sulfobromophthalein sodium (BSP) with perfusion rate (this particular figure is taken from (10) and was originally designed to show the effect of changing hepatic vein pressure (P_v) as compared to that of changing portal venous pressures upon this particular performance).

(Figure 3) (10) in which the isolated rat liver was perfused at different rates and the extraction fraction measured either for chromic phosphate colloid or for tracer doses of radio BSP, shows a most important fact: The extraction fraction is *not* a constant throughout the range of tissue perfusion rates employed, but rather decreases with increasing rates of blood flow. This appears reasonable if you remember that it takes time to transfer any substance from the blood to whatever elements of the liver are to take it up; as the blood flows faster, there is simply less time available for this process so that each particle of blood stands to lose less of the material it carries.

If one wishes to consider the net effect of increased blood flow and decreased extraction fraction upon hepatic clearance, one merely has to plot the product of tissue perfusion (more basic in the present context than liver blood flow, and proportional to it as long as the liver mass is constant) times the extraction fraction (Figure 4) (11). The result, shown this time for the case of chromic phosphate colloid, reveals two extreme zones: one, at low perfusion rates, where extraction fractions are relatively high and the fractional variation in this parameter is small, so that

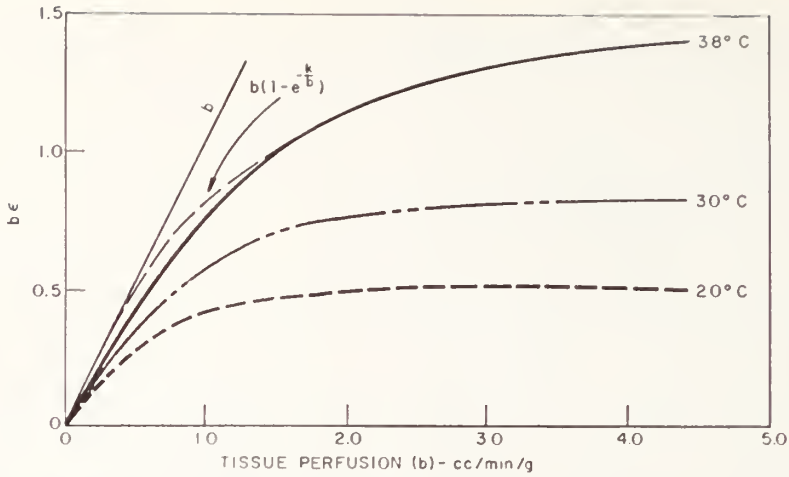

FIG. 4. Effect of variable perfusion rate, and perfusion temperature upon hepatic clearance of chromic phosphate colloid (proportional to tissue perfusion, b, times extraction fraction, ε, since liver mass is constant) (from (11)).

clearance is nearly proportional to tissue perfusion rat. The other zone, at high rates of blood flow, is characterized by an extraction fraction which varies nearly as the reciprocal of the perfusion rate so that the product of the two becomes nearly constant. Consider the effect of partial hepatectomy upon the value of the hepatic clearance in each of these extreme zones: for the former situation, where the product of tissue perfusion and extraction fraction varies as the tissue perfusion, the nearly constant total hepatic blood flow rates observed before and after partial hepatectomy imply that tissue perfusion changes as the reciprocal of the residual liver mass; thus, the amount of substance cleared per unit mass of liver tissue is increased in just the same proportion by which the total mass available to do the clearing is reduced, and total hepatic clearance remains just about unchanged (12). At the other extreme, the product of tissue perfusion and extraction fraction, i.e., the amount of substance cleared per unit tissue mass, has become nearly constant and hence clearance has become almost directly proportional to the residual liver mass. The absolute values of tissue perfusion involved in the example shown are such that the physiological range of liver blood flows corresponds to a zone in-

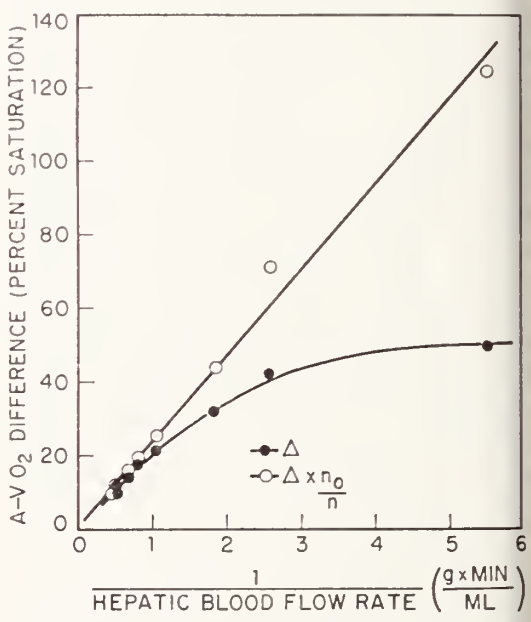

FIG. 5. Oxygen uptake of the perfused rat liver preparation as a function of the reciprocal perfusion rate (Δ—A-V O_2 difference, n/n_0 is the perfusion fraction as a function of perfusion rate based on the data and calculations of (17). Δ divided by the perfusion fraction when multiplied by perfusion rate is the oxygen uptake rate of the functional liver mass) (from (16)).

termediate between these two extremes. Lowering the hepatic blood flow to achieve phenomena characteristic of the low tissue perfusion zone described above gets into

complications due to the shutdown of some of the vascular pathways (cf. (13)) and is not good for livers (the effect upon clearance as indicated as the solid line in the Figure 6, contrasts with the dashed lines for the "theoretical" values and will occupy us more at length further on). Until recently we thought that the high tissue perfusions required for a close approach to constant clearance were simply not attainable in vivo. Recent observations on induced anemia within or without decompression chambers encourage us to think that we can manipulate this parameter more extensively than we had suspected, but have not yet been applied to this particular problem.

There are, however, two other ways of establishing a situation which formally in some respects resembles the high tissue perfusion situation of the examples considered so far. The first of these involves saturation of the uptake capability of the liver with respect to the test substance. A good example is the case of BSP at high blood levels. The complex chain of events which result in the transfer of this dye from blood to (or past) some depot site in the liver, and to the bile, undergoing transformation to amino acid conjugates on the way, includes at least two steps which have a limited capacity; one of these involves biliary secretion and does not concern us here. The other quite likely involves the actual transfer of the dye across the cell boundary. In the dog this situation is readily illustrated on analysis of continuous infusion data (14): As one examines an ascending series of infusion rates beginning at infusion levels resulting in fairly low steady plasma BSP levels, the extraction efficiency decreases with increasing blood levels. It does so, however, more slowly than the plasma levels; the hepatic clearance thus increases, through more slowly than the plasma levels. There comes a point, however, where the rate of decrease of extraction fraction comes to equal the rate of increase of the plasma levels. Further increase in plasma level then fails to result in augmented clearance, and on increasing the infusion rate beyond this point, the liver can no longer remove enough dye to establish a steady state at any plasma concentration. This point has been designated as L_{max} (cf. (15)) because, all other things being equal, this critical infusion rate is proportional to total liver mass, just as was the limiting clearance for the preceding group of substances, and formally for the same reason. Extraction efficiencies for BSP in this region are so small that their direct measurement is most unsatisfactory, and seems to me a dubious basis for any sort of elaborate theoretical or clinical development; on the other hand the plasma levels are extraordinarily sensitive, since the "steady" state level for any infusion rate beyond the limiting is "infinite" (at least in the absence of too much extrahepatic uptake) or in practice unattainable.

Another situation in which the measured performance of the liver is directly proportional to the functional liver mass is encountered whenever one deals with a substance which is consumed by the liver as part of its normal everyday metabolism, so to speak, and which because of its relation to other hepatic metabolites is not rate controlling once it is available in adequate minimal amount. Perhaps, the classical example of such a substance is molecular oxygen. The relations between tissue perfusion and oxygen uptake of the isolated perfused rat liver supplied with whole blood at a high level of oxygenation here are as follows (16): At high perfusion rates the A-V oxygen difference is indeed inversely proportional to the perfusion rate, as predicted for a substance consumed at a constant rate by the tissue. At low perfusion rates, however, very considerable discrepancies are noted, the organ consuming considerably less oxygen than predicted from the values observed at the higher perfusion rates (Figure 5). We feel that this is nicely in line with other observations which, at a much earlier date, we had interpreted as evidence of a progressive shutting down of parts of the hepatic vascular tree under the perfusion

conditions which give rise to such low perfusion rates in vitro (13, 17). The lines of experimentation which severally and conjointly point in this direction include changes in bile flow rates, changes in the blood volume determined by single passage distribution methods (transient analysis), and deviations from theory of the efficiency of chromic phosphate colloid uptake. From such measurements one can in fact deduce the perfusion fraction, that is the fraction of the possible vascular channels in a given liver actually perfused under any given perfusion conditions. Application of the figures thus derived to the observed hepatic oxygen uptakes at low perfusion pressures leads to corrected A-V differences (observed values divided by the perfusion fraction) which turn out to rigidly satisfy the condition of reciprocity between perfusion rate and extraction fraction which should obtain if oxygen uptake in the perfused portions of the tissue were indeed constant. It must be apparent that such a procedure is tantamount to a definition of functional liver mass, in the present context at least, of that portion of the liver actively supplied with blood at the moment of testing. The fact that substantially the same function is obtained for the relation bewteen function hepatic mass and perfusion rate by using as the criterion either oxygen uptake, or chromic phosphate could uptake, or blood volume, or bile flow, or perfusion resistance would seem to lend considerable assurance to our interpretation of this particular situation. It implies that the diffusion distances between successive lamellae of parenchyma are such that the oxygen supplied via one sinusoid does suffice to maintain a measurable degree of respiration, or to sustain bile secretion in neigh-

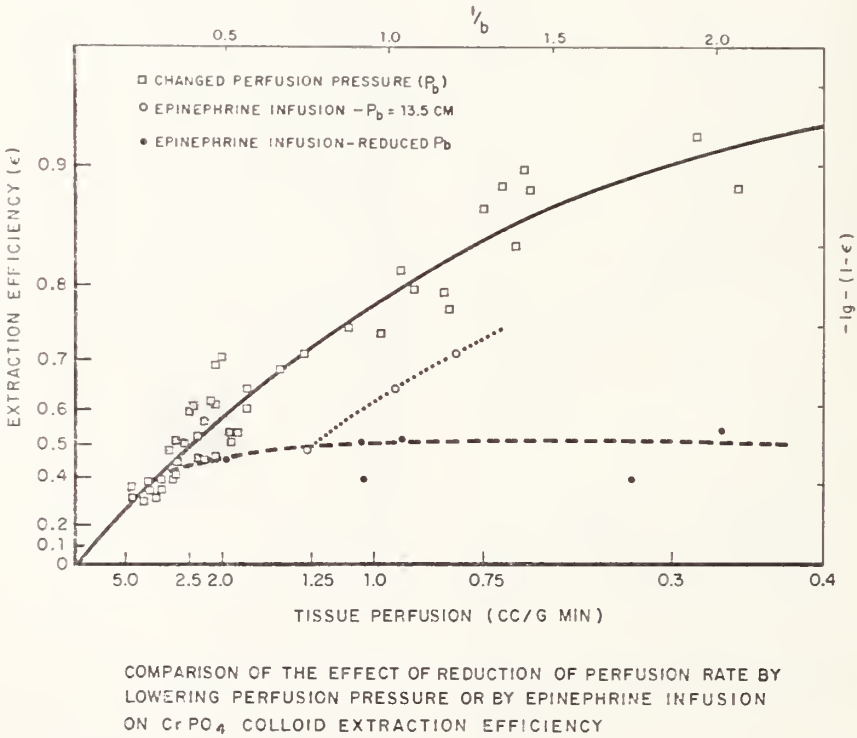

FIG. 6. The effect of epinephrine infusion upon the extraction fraction for chromic phosphate colloid in the isolated rat liver preparation. The several curves refer to alternative mass of reducing the perfusion rate (from R. W. Brauer—Multiple Parameters Needed to Adequately Describe the Status of the Hepatic Circulation, in Hepatitis Frontiers, F. W. Hartman, G. A. Lo Grippo, J. G. Mather, and J. Barron, eds., Little Brown and Co., Boston, 1957).

boring lamellae not directly supplied by that sinusoid; only thus can one readily explain the concordance of the oxygen uptake data with the chromic phosphate colloid ones which can be attributed with assurance to changes in the effective Kupffer cell surface area presented to the moving blood stream.

To add one more illustration of the concept of functional liver mass, consider the effect of epinephrine infusions upon chromic phosphate colloid uptake by the isolated rat liver (Figure 6). This agent, as you may recall, has been shown in vivo to bring about the transition from a diffuse to restricted hilar distribution of portal venous blood flow (4) and would be expected to lead to a reduction of the functional liver mass. In vitro, as you can see, the effect of such a procedure is to reduce the colloid extraction efficiency in such a manner that at a perfusion rate of only 1 ml/g/min the epinephrine treated liver behaves like the normal perfused liver at a perfusion rate roughly twice as large—precisely what would be predicted if the functional liver mass had been reduced to about half of the total liver mass. I might note in passing that last week I was shown data for the intact dog which indicate that the same effect can be observed there using silver plated gold colloid as the test substance (18).

It might be useful to summarize these relations in diagram form (Figure 7). This shows that the concept of hepatic clearance can be successively dissected by the use of the concepts we have developed above, until one arrives at a form which allows one to separate changes in intrinsic hepatic function (i.e. those not dependent on blood flow distribution) from changes in the functional hepatic mass, which are associated with alterations in blood flow distribution. Theoretically, the methods for effecting such an analysis are at hand, and have been illustrated in our preceding discussion. In practice, things are not quite so easy for two reasons. In the first place, in keeping with the problem I posed at the beginning of this presentation, I have confined my analysis to the modification of measurements of liver performance by circulatory changes. This, however, does not imply that these are the only parameters capable of modifying the functioning of the liver. Liver injury of many types, or even changes in nutritional status well within the range of the physiological can assuredly modify any one of the indices we have discussed and complicates the establishment of the necessary baselines for ready application of some of the methods discussed. However, I hope I have succeeded in making the point that the hepatic circulation is quite capable of producing extensive changes in the functional performance, and that the establishment of the circulatory status of the liver is indispensable if any further analysis of hepatic function is to be meaningful. A second point to be considered in relation to the analysis of hepatic clearances is that the measurements I have presented to you as illustrations were obtained under rather special conditions, established with a view to allowing substantially complete control of all the pa-

(Hepatic Clearance)

(Total Hepatic Blood Flow) × (Extraction Efficiency)

(Liver Mass) × (Mean Tissue Perfusion) × (Hepatic Extraction Efficiency)

$$\underbrace{\begin{bmatrix}\text{Liver}\\ \text{Mass}\end{bmatrix} \times \begin{bmatrix}\text{Perfusion}\\ \text{Fraction}\end{bmatrix}}_{\text{Functional Liver Mass}} \times \underbrace{\begin{bmatrix}\text{Effective}\\ \text{Tissue}\\ \text{Perfusion}\end{bmatrix} \times \begin{bmatrix}\text{Hepatic}\\ \text{Extraction}\\ \text{Efficiency}\end{bmatrix}}_{\text{Specific Hepatic Clearance}}$$

Fig. 7

rameters which seemed pertinent to the analysis at hand. In studies on intact subjects a number of additional complications present themselves, and at times may call for some rather fancy experimental footwork if they are not to falsify or obscure the meaning of the results obtained. Among these in particular one might call attention to changes in liver temperature—some liver functions, such as for instance bile secretion (19), have extremely high temperature coefficients so that measurements obtained under conditions where temperature control cannot be assured (as in forcibly restrained rats or rabbits, or in anesthetized subjects) must include liver temperature data to be meaningful;—the fact that hepatic vein sampling by catheter does not necessarily provide one with truly representative samples of hepatic vein blood (see for instance the complicated results obtained when attempts were made to measure extraction efficiencies of substances administered by portal vein (20), (21) and the contortions various workers have gone to overcome this particular problem); and finally the problem of defining the proper blood volume to enter into calculations based on time-blood concentration curves derived from single injection experiments (for substances which are very efficiently removed the proper value is the total blood volume minus the splanchnic volume (22), while for substances removed quite inefficiently it is the total blood volume—no really rigorous treatment seems to exist for the intermediate cases). Other instances could be produced readily, but these will suffice to indicate to you the kind of problems which arise to bedevil the investigator in this field and which are apt to call upon all the experimental and theoretical resources at one's command if meaningful results are to be produced.

I should like to close this discussion of the role of the hepatic circulation in the regulation of various aspects of liver physiology by turning attention to the relations which can be discerned between the circulation of the liver, and liver injury, respectively the defense of liver integrity. At this point we leave the area of what I believe is fairly well mapped territory and enter a realm where our present preoccupation is with the finding and identifying of landmarks; thus, I shall not even attempt to present to you anything like an outline of knowledge achieved, but rather place before you as promising a statement of the case as I can muster at the present time and trust to the future to provide the knowledge which will allow a more equitable statement.

A good way of posing the central problem in this context seems to me to take a brief look at the data bearing upon the effect of one class of hepatotoxic agents, namely, the chlorinated hydrocarbons. Both chloroform and carbon tetrachloride have been recognized for a long time as agents capable of producing severe liver injury. Furthermore, a considerable body of evidence indicates that the pathological changes which follow upon the exhibition of either of these agents can be greatly alleviated by augmenting the supply of oxygen to the tissue, and that they can be enhanced either by impairing the hepatic oxygen supply or by enhancing the oxygen requirements of the liver while holding the oxygen supply relatively constant (cf. e.g. (23)). Of particular pertinence to this gathering is perhaps the fact that one of the earliest convincing studies in this area was performed by one of your own colleagues, Dr. Ravdin (24). His papers on this subject are of additional interest in that they contain what seems to have remained an isolated reference to the fact that the application of oxygen during chloroform anesthesia results in some degree of separation of the morphological changes (which are largely relieved) from at least one biochemical change (the hyperglycemia—which is not affected). From such observations one might superficially hypothesize that the real basis for the action of chloroform or carbon tetrachloride is the production of tissue hypoxia in the liver, and that the remaining effects (ignoring such observations as those on the hyperglycemia) are to be

considered as secondary sequelae, no different from the effects of any other form of hepatic hypoxia. Following this line of reasoning, several papers (cf. e.g. (25)) have appeared recently claiming that the administration of these agents brings about a widespread sympathoadrenal discharge which, by reducing hepatic blood flow, is said to set in motion the vicious circle of liver injury leading to circulatory impairment, leading in turn to hypoxic liver injury, which leads to further circulatory impairment which aggravates the injury, and so on to the destruction of the parenchyma, or to resolution of the lesion if the circle can be broken in time. In support of this view, it is reported that sympatholytic agents as well as cordotomy at a level which will interrupt the splanchnic supply can greatly moderate the toxic effects of carbon tetrachloride. Without entering into a detailed criticism of these stimulating experiments, it is pertinent for our argument to point out that most recent observers who have performed their experiments while guarding themselves against artifacts due to the anesthetic effects of these agents have either failed to see any vasoconstriction following the administration of these chlorinated hydrocarbons (26, 27), or—as in our own case—have seen such changes only after the characteristic cloudy changes in the liver have become evident, and long after the earliest biochemical changes have become demonstrable in the tissue (28). To clinch this argument, we have recently conducted a series of experiments in which the isolated rat liver, perfused with highly oxygenated blood, and at rates which are somewhat greater than those obtaining in the rat liver in situ in the intact animal, was exposed to chloroform in concentrations ranging from what in vivo are barely subanesthetic to lethal levels (29). Under those conditions, we can now state "without fear of successful contradiction" that chloroform exposure not only does not induce any vasoconstriction, but rather a quite perceptible vasodilatation (this, of course does not in any way prove

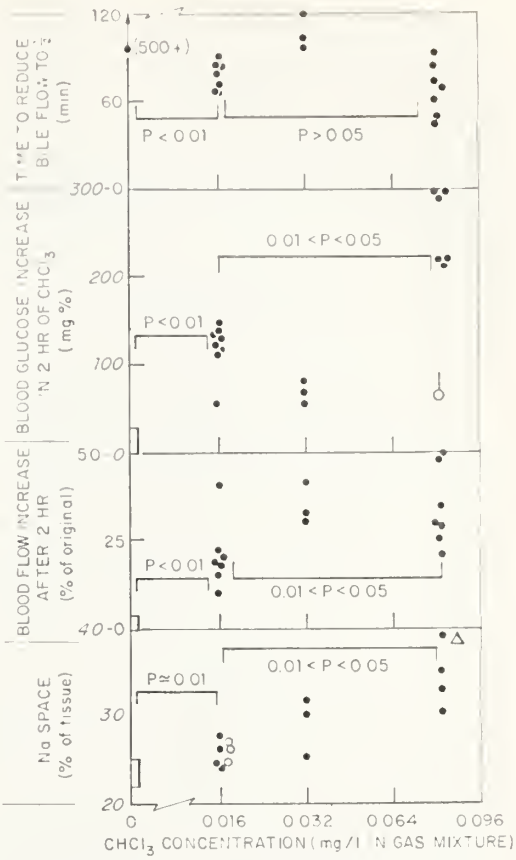

FIG. 8. The effect of $CHCl_3$ administration on various parameters describing the status of the isolated rat liver preparation (from (29)).

that the same thing *must* occur in the intact animal); at the same time, and this is the crux of the matter, there is a very marked reduction in bile secretion rate and a massive increase in blood glucose levels in the perfusion system (Figure 8). Other changes which accompany this sequence of events include a marked increase in the tissue sodium space, and the appearance of histologic changes similar to those seen in intact animals after comparable periods of chloroform exposure. It is difficult, in view of these findings to escape the conclusion that the primary chloroform lesion can be induced under conditions which involve neither ischemia nor any type of hypoxemic anoxia. This conclusion is strengthened by such important differences between the chloroform injured liver and the liver

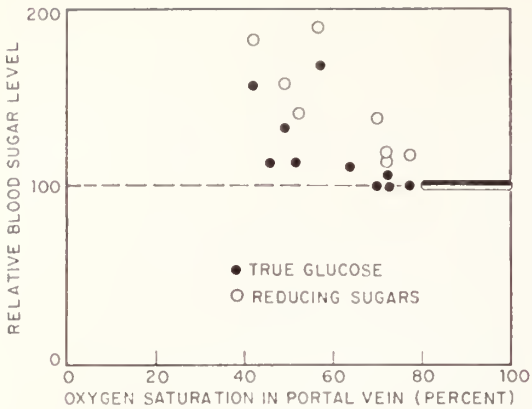

FIG. 9. Blood sugar level changes in the isolated rat liver preparation exposed to various degrees of hypoxia (from (16)).

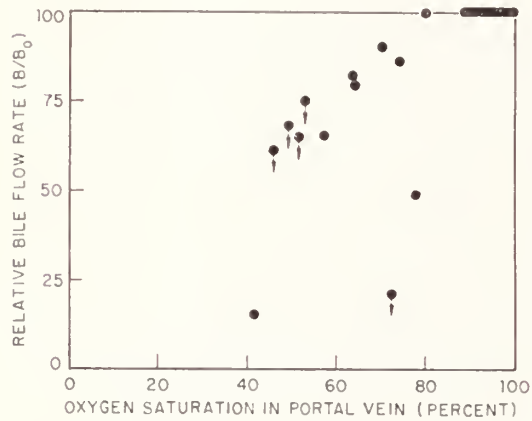

FIG. 10. Bile flow changes in the isolated rat liver preparation exposed to various degrees of hypoxia (arrows indicate progressive bile failure (from (16)).

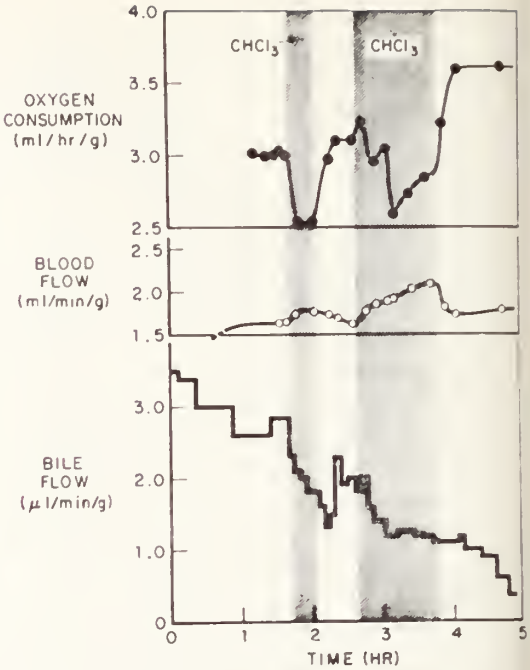

FIG. 11. Effect of $CHCl_3$ exposure on blood flow, oxygen uptake and bile secretion of the isolated rat liver, showing differences in the degree reversibility of the several changes observed.

subjected to degrees of hypoxia producing comparable changes in bile flow, as the very large glucose release in the former contrasted with a marginal glucose release in the latter situation (Figures 9 and 10). A histotoxic effect of chloroform is certainly also in accord with recent biochemical observations indicating very early changes in lipid handling by livers of animals exposed to the closely related carbon tetrachloride (30).

If on the basis of all these observations one concludes that the primary biochemical lesion produced by these chlorinated hydrocarbons is not preventable by assuring the most adequate tissue oxygenation, one is driven to the conclusion that the well documented effects of oxygen administration, and by inference of the procedures aimed at eliminating the circulatory effects of the sympathetic innervation of the liver, must be based upon a modification of the subsequent fate of cells carrying the primary, biochemical lesion inflicted by these chemicals. What precisely will emerge from a quest for these factors influencing the recovery of injured cells, it is too early to say. Some of the directions in which such a search might take one can, however, be discerned even at this time. On the cytochemical side, promising indications are available pointing to an early involvement of the microsomal components (28), followed somewhat later by changes in the structure and in the composition of the mitochondria (31, 32). The time course of these changes is only incompletely mapped out at present, and it is too early to do more than speculate concerning causal relations, and hence concerning the role of one or other

substance brought to the cells by the blood stream and conceivably involved in steering the course of the intracellular changes. On a less sophisticated plane, there is some interesting evidence concerning a dissociation of various indices of altered liver function in the presence of chlorinated hydrocarbons. I have already alluded to Dr. Ravdin's old observations showing that oxygen therapy can affect mortality as well as the tissue pathology, while the characteristic hyperglycemia is not so modified. While in the intact animal one might look for an explanation in terms of complicating factors which might account for the different behavior of these indices (such as a sympathoadrenal discharge), one can hardly invoke such an explanation in the case of the isolated liver. In that situation some further separation of "reversible" and "not so reversible" effects has been found (Figure 11). Among the four non-morphologic effects of chloroform exposure studied so far, namely vasodilatation, hyperglycemia, decreased oxygen consumption, and decreased bile secretion, bile secretion alone appears to be irreversibly, and usually progressively impaired, following a downhill course even after withdrawal of the chloroform; glucose dumping is generally stopped but not reversed (quite possibly for endocrinologic reasons), while the vasodilatation as well as the oxygen consumption quickly return to preexposure levels, or, in the case of oxygen consumption, often to significantly higher levels than prevailed before the period of exposure. It would seem plausible to look among those indices which fail to return to baseline values for future keys to external factors which might aid the course of cellular recovery. A further situation which appears potentially interesting and important appears to me to be a profound difference we have discovered between the isolated liver and the liver in situ with respect to their ability to restore normal bile flows following periods of hypoxia.

In the former, hypoxia which will induce a gradual decrease of bile secretion such that at the end of one hour bile flow has been reduced to about 50 or 60% of its initial rate, results in such changes that restoration of high levels of blood oxygenation not only fails to reverse the change incurred during the hypoxic period, but does not even arrest a further progressive falling off of bile flow, terminating most commonly in complete acholia. By contrast, hypoxia which in the intact animal elicits comparable or even more severe acute bile flow reduction, when relieved by oxygen inhalation, is promptly followed by complete restoration of preexposure bile secretion rates. This situation appears to lend itself singularly well to experimental dissection which, we hope, should soon shed further light on factors either inherent in vascular anatomy or in blood composition, which make for reversal of lesions of this type and for the recovery of the jeopardized cells.

This list of promising leads could surely be extended a good deal further; thus, the cordotomy and dibenamine effects upon the toxicity of chloroform surely belong here, as does the complex body of observations concerning the effect of hepatic artery ligation in different species, or in the same species under different modes of treatment. However, enough has perhaps been said already to indicate what are my thoughts concerning an area of inquiry which at the present time needs more data rather than more speculation.

In 1951 in a brilliant series of talks Prof. Himsworth summed up what then appeared a fair statement of knowledge on this general subject by suggesting a vicious circle of liver disease (33). In that view impaired liver circulation—however brought about—would lead to liver injury, which would entail further impairment of the hepatic circulation, which would renew the cycle. Today, a decade later, I feel that the old scheme calls for revision. I suggest a sequence of events in which primary liver injury, however produced, leaves the parenchymal cells in a jeopardized position where either recovery (or even adaptation to the originally injurious condition) or progression on the path to necrobiosis, are open

to it. Which path a particular cell will travel depends in considerable measure upon the environment in which it finds itself following the insult, an environment which, as we now know, is largely conditioned by the circulatory status of the liver. That progressive cell injury in the liver may well entail deterioration of the circulation, and hence initiate at this point a vicious circle of the type envisioned by Prof. Himsworth appears altogether possible. For my own part, however, I feel that it is in the area of the recovery of the liver cell from injury, and in the role of the hepatic circulation in this process, that the most exciting advances in this field are to be looked for in the near future.

(The opinions or assertions contained here are those of the author and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.)

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Mouse Polyoma Virus Infection[1]

By WALLACE P. ROWE, M.D.[2]

A CARDINAL principle of virus research is that progress in the study of an agent is primarily dependent on the sensitivity and speed of the indicator system available for detecting infection with the virus. As a corollary to this, a virus indicator system which relies on the production of disease may well be far less sensitive than one which is based on some other index of infection, regardless of whether the infection results in overt disease or not.

The importance of these statements can be illustrated by the history of work with poliomyelitis virus. The virus etiology of this disease has been well established for 52 years; however, for four-fifths of this period the only means for detecting the virus was inoculating monkeys and observing them for paralytic disease. Much information was acquired with this type system, but the results were obtained only with great effort, uncertainty, and expense. The development of tissue culture assay systems in 1948, obviated most of the difficulties. An infectious process, not subject to the many variables which may influence the occurrence of clinically obvious disease, became the indicator of virus activity; the sensitivity and speed of virus detection were increased; and the rapid accumulation of significant and verifiable data is familiar to all.

In the field of tumor viruses, the situation is much like the early era of poliovirus research. Again, for 50 years it has been known that certain viruses result in production of tumors, and, conversely, that certain tumors occurring spontaneously in animals are caused by viruses. However, studies of these viruses have presented generally far greater obstacles than the monkey assay for poliomyelitis virus, the reason being that the endpoint for detecting virus activity has been production of disease, in this case tumors, and such induction of disease in many cases has required observation periods of many months or several years. Laboratory strains of some tumor viruses have been developed which give rapid induction of tumors; namely, Rous sarcoma virus, the erythroblastosis and myeloblastosis viruses of the avian leucosis complex, and the Friend mouse leukemia virus. The sensitivity of these methods still leaves much to be desired, and the procedures which are useful for study of these well-adapted laboratory strains of virus are not applicable to the naturally occurring strains of virus in spontaneous tumor cases in the field. For example, the Rous sarcoma virus of chickens was described in 1911, and extremely sensitive and useful laboratory systems have been developed for its study. However, isolation of fresh strains of this virus from spontaneously occurring sarcomas in chickens is a relatively rare event, and despite the systems available, very little has emerged on the natural history of infection.

Within the last few years a tumor virus has been discovered which is not subject to these severe technical limitations, but whose laboratory behavior is as readily studied as some of the viruses of classical acute infectious disease, and which consequently has provided one of the first opportunities to study with any degree of exactness the epidemiology and natural history of a tumor virus.

The mouse polyoma virus was first encountered as an incidental finding in the

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study of mouse leukemia. Both Dr. Ludwig Gross of the Bronx Veterans Administration Hospital, and Dr. Sarah Stewart, of the National Institutes of Health, observed that when filtrates of leukemic mouse tissue were inoculated into newborn mice, in addition to a greatly increased incidence of leukemia, there was significant occurrence of an unusual mixed tumor of the parotid salivary glands, occasional subcutaneous fibrosarcomas, and tumors of the adrenal medulla. In these initial studies, the incubation period for tumor development was 8 to 12 months, response was erratic, and to all appearances, study of the agent was destined to follow the familiar pattern of slow, painstaking garnering of information as with other long incubation period tumor viruses.

However, a dramatic development came when Dr. Stewart, working collaboratively with Dr. Bernice Eddy, found that the virus could be propagated in tissue cultures of monkey kidney or chick embryo cells. When inoculated into newborn mice the cultured virus produced a highly dramatic array of tumor response. In addition to salivary gland tumors, which were seen in almost all mice, neoplasms of many other tissue types also developed, particularly mixed tumors of the respiratory mucous glands, epithelial tumors of the skin, subcutaneous fibrosarcomas, renal sarcomas, osteosarcomas, thymic epitheliomas, carcinomas of the mammary gland, as well as many others. However, leukemia was not induced by the tissue culture preparations. Also, the virus produced tumors in other rodent species, inducing fibrosarcomas and hemangioendotheliomas in suckling hamsters, sarcomas in rats, and fibromas in rabbits.

In further exploiting this finding, Drs. Stewart and Eddy found that the virus would not only propagate well in mouse embryo tissue cultures, but that its growth in this tissue was accompanied by a characteristic cytolytic degeneration of the cultures, or cytopathic effect. This most important finding permitted the virus to be detected and quantitated by means of an *in vitro* tissue culture system, using the appearance of cytopathic effects as the endpoint rather than tumor response—an almost unprecedented finding with tumor viruses.

Thus the work of Stewart and Eddy not only raised many important questions concerning the role of this virus in the problem of spontaneous tumor occurrence in mice and other species, but also, by means of the *in vitro* techniques, provided the possible tools for answering such questions. With this possibility in mind our laboratory, under Dr. Robert Huebner, Dr. Janet Hartley, and myself, undertook a program to study this virus from the standpoints of developing simple diagnostic serologic tools, studying the natural history of the infection in mouse populations and possibly other species, and evaluating the importance of this virus as a cause of spontaneous tumors.

A key technique for studying infection with the polyoma virus was provided when it was found, together with Dr. Eddy, that the virus hemagglutinated guinea pig and other species erythrocytes. The hemagglutination by this virus resembled that of the influenza viruses in many respects; the enzymatic activity of influenza virus and of cholera vibrio filtrates, which destroyed the receptors on red cells for the influenza viruses, also destroyed the receptors for the polyoma virus.

The primary importance of the hemagglutination phenomenon with polyoma virus lay in its usefulness as a tool for demonstrating antibody, since it was found that the virus is a highly potent antigen. Mice inoculated with the virus uniformly develop antibody, generally in high titer, and the antibody persists for an indefinite period. The antibody can be demonstrated by hemagglutination-inhibition, complement fixation, or tissue culture neutralization tests, but the hemagglutination inhibition test is most rapid and sensitive. When groups of mice are inoculated parenterally with serial dilutions of a preparation of polyoma virus whose tissue culture infectivity titer is known, and their sera are tested for antibodies after three or

four weeks, it is found that the mice respond with antibody formation when inoculated with virus dilutions corresponding to one tissue culture infectious dose. Although mice respond with tumor formation only if they are inoculated within the first few days of life, they respond with formation of antibody to minimal dosage of virus regardless of age. Thus, the rapid development of resistance to tumorigenesis that occurs with aging is completely distinct from resistance to infection. As far as is known the infection of the older animals is completely subclinical. The fact that mice will respond with antibody formation following inoculation with minimal amounts of virus has been extremely useful as a technical procedure for detecting presence of virus in a specimen.

With the availability of well evaluated serologic and virus detection procedures, it became possible to survey various populations of laboratory and wild mice to determine if the agent could be detected as a nautral infection of mice, and if so, to analyze the patterns of distribution of infection to determine its mode of spread and survival.

Serologic surveys of laboratory mouse colonies gave a very clear-cut pattern of results. Antibodies to the virus were found to be highly prevalent in some colonies, in low frequency in others, and totally absent in others. Laboratory mouse breeding colonies can be grouped roughly as follows: small breeding colonies maintained by an investigator in proximity to his experimental animals; large animal production colonies consisting of conventionally reared animals with no contact with experimental animals; and "specific pathogen free" and "germ free" colonies, consisting of descendants of mice obtained by Caesarean section reared under various strict isolation conditions. In the first type of colony polyoma virus infection was frequently encountered, with highest levels of spontaneous infection in the colonies in contact with experimental work involving deliberate or unintentional inoculation of polyoma virus into newborn mice. Among the animal production colonies, extreme variations in antibody frequency were encountered, ranging from zero to essentially one hundred percent of retired breeder mice infected. The findings in the third type colony are particularly significant, in that none of the Caesarean-derived colonies was infected, even though several had been derived from heavily infected stocks. Within the infected colonies, the only population attribute significantly associated with frequency of infection was age. Sex and genetic strain were not correlated in the least with frequency of infection. The latter observation is particularly important in view of the strong impression of strain specificity of infection produced by the repeated association of the virus with leukemia in the AKR mouse strain. It now appears highly probable that this association was the spurious result of working with infected mouse stocks.

All evidence from the serological testing of laboratory mouse colonies indicated that infection with polyoma virus was dependent on the degree of environmental contamination with the virus, and that infection is acquired postnatally.

Comparable evidence for focal areas of infection was found in surveys of wild mouse populations. Trapping surveys conducted in New York City and on farms in Montgomery County, Maryland, revealed that some environments continually harbor infected mice, while in other areas the mice are free of infection. The limited evidence available at present does not indicate that other species living in the infected areas acquire the infection.

Another aspect of polyoma virus infection which has contributed much to the clarification of the above epidemiological findings is the study of the infectious process in the individual mouse. The pattern of growth of virus following inoculation into newborn mice is quite unique in comparison with that of other tumor viruses similarly studied. The general pattern with tumor viruses such as mouse leukemia viruses, the Rous sarcoma, the Shope papilloma and the mouse mammary tumor agent appears to be a limited degree of

viral replication during the latent period between acquisition of the agent and appearance of tumor, with active viral growth accompanying growth of tumor. In contrast, polyoma virus grows to very high titer in most tissues of the suckling mouse within 7 to 14 days after inoculation, then declines in amount and remains in relatively low titer indefinitely; there is no increase in virus activity with appearance of tumor. The mice infected as newborns excrete large amounts of virus in urine and saliva, many for prolonged periods. Weaned mice show a qualitatively similar virus growth pattern, but the degree of virus growth is greatly restricted, and excretion of virus is usually minimal. However, an infrequent mouse infected as a weanling does excrete large amounts of virus and can serve to infect contact mice.

In this connection it should be noted that the virus growth pattern in the hamster shows a pattern similar to that in the mouse, but with a very important quantitative difference. The virus attains peak infectivity titer at 5 to 7 days, the peak growth being much lower than in the mouse; after the second or third week, the virus is no longer detectable, and tumors appearing after this time do not yield virus.

From these various findings, we now picture the natural history of polyoma virus in terms of the virus being basically an indigenous agent of wild mice, being maintained in certain areas where the environment, particularly communal nests, has become seeded with infected excreta. Laboratory colonies become infected by contact with wild mice, by food or bedding contaminated by wild mice, or by importation of infected mice or reagents from other laboratories. In the laboratory the agent is maintained in many instances by exposure of breeding stocks to experimental animals inoculated with contaminated materials. In the absence of such artificial exposure, a colony can maintain the infection only if there is a very large, dense population.

Despite the remarkable tumorigenic capacities of polyoma virus under precise laboratory conditions, in its natural occurrence in laboratory and wild mice, it is not a signficant cause of spontaneous tumors. Spontaneously occurring parotid tumors of the type caused by polyoma virus have been observed on very rare occasions, but almost exclusively in mice raised in close contact with laboratory work with the agent. The failure of the virus to cause spontaneous tumors can be explained by the rapid development with age of resistance to the tumorigenic effect of infection, protection by maternal antibodies, infection by low dosage and by way of inhalation, which is an ineffectual route for obtaining tumor response.

The unique features of the pathogenicity and pattern of infection of polyoma virus have had a remarkable impact on virologists' conceptions of tumor-inducing viruses and of means of approach to the question of tumor viruses in man.

In this respect three aspects of the infection are of particular significance: the crossing of species lines, the phenomenon of peak virus growth long before the appearance of tumor, and the applicability of classical virologic techniques to study of the agent and its natural history. Taken together, these three concepts lead to important negative conclusions: 1) that the familiar viruses of humans and their associated animals cannot be excluded from consideration as possible tumorigenic agents merely because they produce acute type infections and are readily studied in the laboratory; and 2) that because a virus cannot be extracted from a tumor does not mean that the tumor was not caused by a virus. These conceptions remove the theoretical objections to formulation of a vast number of hypotheses of possible etiologic relation between various known viruses and certain tumor types; however, by their very nature these hypotheses are difficult to test. How can the laboratory worker or epidemiologist examine such an hypothesis as for example, that "some or all carcinomata of the tonsil are caused by prior infection with certain adenoviruses"? In addition to raising such questions, the polyoma virus studies have pro-

vided several possible approaches to their solution. For the epidemiologist, a practical approach may lie in retrospective surveys, using serological procedures, to compare the frequency of previous adenovirus experience, as in our example, in cases of carcinoma of the tonsil as compared with a carefully selected matched group of controls. Even with highly prevalent agents, which almost all persons acquire during childhood, an analogy with polyoma virus infection provides an approach; there is evidence that tumor response to polyoma infection of mice is associated with high antibody titer, while the antibody titers in animals which do not develop tumors are lower. Thus serologic surveys on a quantitative basis may be a most fruitful approach.

For the laboratory worker, polyoma virus studies have provided a procedure which appears to be a most promising tool for the evaluation of the possible oncogenicity of classical viruses, namely, organ cultures. Dr. Clyde Dawe has demonstrated that organ cultures of mouse salivary gland tissue undergo marked proliferative changes after infection with polyoma virus; in contrast to the intact animal, the proliferative response is not inhibited by the immune status or age of the donor animal. Thus this procedure offers a means of testing within species, without using whole animals and without some of the physiological and immunological restrictions of the intact animal. Application of this procedure to various combinations of viruses and human organ cultures may disclose tumorigenic systems of importance in human medicine.

Polyoma virus has provided a great stimulus to investigation of the possible viral etiology of human cancer, and has provided some important lines of approach; but the study of this agent has also served dramatically to illustrate that isolation of a tumor virus is only an initial step, and that evaluation of its importance as a cause of disease ultimately depends on the application of classical epidemiologic methods.

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The Sickness of Philoctetes[1]

By JERRY D. HARRELL, M.D.[2]

WHEN the Greeks under the leadership of Agamemnon were about to sail forth against Troy, it became known that an oracle had ordered them to make a sacrifice at the altar of the goddess Chryse. This was supposedly located on a small island in the Aegean Sea, near the eastern shore of Lemnos. Philoctetes, a renowned archer and leader of a contingent from that area of ancient Greece known as Malis, agreed to act as guide for the fleet of Agamemnon and led it to the isle of Chryse. There, according to the epic poem of Stasinus of Cyprus, he was bitten by a serpent. His cries were so terrible that it became impossible to perform the religious rites, which required the absence of all ill-omened sounds. The suffering Philoctetes was thereupon conveyed to the neighboring coast of Lemnos, put ashore, and abandoned.

The Greeks sailed on to the Asiatic shore of the Hellespont to begin their siege of Troy. Ten years of indecisive fighting elapsed. Philoctetes was still languishing on Lemnos; his former comrades were still encamped before the walls of Troy, unable to bring about its capture. The despondent Greek leaders were told by the captured seer Helenus that Troy could only be taken if Philoctetes, possessor of the bow and arrow of Heracles, were rescued from Lemnos. Odysseus and Neoptolemus, the son of Achilles, accordingly went to Lemnos and brought Philoctetes back with them. In the fighting that followed, he killed the Trojan hero Paris and shared in the glory of the victory over Troy.

It was upon this epic story that Sophocles based his tragedy, *The Philoctetes*, which was first performed in Athens in 409 B.C.

In the pages following we shall examine Sophocles' description of the sickness with which Philoctetes was afflicted. While the playwright follows the recorded legend in attributing the Greek exile's suffering to a snake bite incurred at the sanctuary of Chryse, the account of the illness in the play shows a striking resemblance in many ways to an epileptic seizure of the grand mal variety.

My reason for disregarding the diagnosis of Sophocles is that there is a good likelihood that the story of Philoctetes, like many of the other epic tales which have come down to us, may have a basis in fact. Frequently the central core of truth was gradually obscured or distorted by the bards who for centuries wandered amongst the Greeks about the Aegean telling and retelling the adventures of the men who sailed against Troy. If the sickness of Philoctetes had been epilepsy, we could much more easily understand the attitude of the Greeks toward him.

Even if the story should not be a reflection of a real epileptic Philoctetes, it is possible that Sophocles, in desiring to present a picture of a seriously ill Philoctetes, abhorred and rejected by his comrades, chose to describe an epileptic attack and thereby added to the dramatic effect.

In connection with our study I should first like to cite several other instances in which present day writers have discerned descriptions of epileptic seizures in the works of the Greek tragedians.

The question arises whether the description of the madness of Heracles and Orestes, etc. can be interpreted as indicating epileptic states. From the modern point of view they could indeed be identified with "dreamy states" of epileptics. In Euripides' *Iphigenia in Taurica*, 281 ff . . . Orestes has illusions and attacks cattle with

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his sword, then falls down, his beard dripping with foam. However, Euripides expressly calls it "mania":

> "πίπτει δὲ μανίας πίτυλον ὁ ξένος
> μεθεὶς, στάζων ἀφρῷ γένειον."

In Euripides' *Madness of Heracles*, 923 ff . . . and Seneca's *Hercules Furens*, 930 ff, the hero is confused and has illusions during which he kills his wife and children. Then he falls to the ground and sleeps; finally he awakes cured, but without memory of the whole episode. Modern psychiatric literature from the 19th century on relates similar actions of epileptics.[3]

Mr. Ainsworth O'Brien-Moore also concludes that Orestes in *Iphigeneia in Tauris*[4] suffered from hallucinations and "something like epilepsy." In the *Orestes* he awakes from a deep sleep with caked foam on his mouth and eyes, and shortly thereafter is seized by hallucinations, during which his eyes roll wildly and his hitherto feeble body is filled with a maniac strength. Here again it appears that Euripides has described for us a physical sickness which is apparently epilepsy, accompanied by hallucinations.

Mr. O'Brien-Moore further states that the madness of Heracles is compounded of a "physical affection like an epileptic seizure, a complicated delusion, and the goddess Lyssa".[5] The author goes on to say that Heracles "shakes his head, rolls his eyes, pants and bellows. We learn further from the messenger that at the beginning of his madness Heracles foams at the mouth and laughs insane laughter, and that at the end of his attack he falls senseless to the ground. These symptoms are on the whole like those of Orestes in the *Iphigeneia*, and all of them individually are concomitants ascribed by the ancients to epilepsy, among which we find listed convulsions, rolling of the eyes, strangling, yelling, foaming at the mouth, and falling senseless."[6] Thus, probably for dramatic effect, Euripides has made Heracles suffer an epileptic seizure although he does not name it as such.

Not unlike the physical signs shown by Heracles are the rolling eyes and foaming mouth of Agave, allegedly due to possession by Dionysus.[7]

Similarly, Drs. Pommé and Scouras have studied the behaviour of the hero Ajax as we have it described in Sophocles' play of that name, and have decided that he had the same illness.

> Nous croyons qu' Ajax ne réalise pas simplement un type de paranoïaque mais encore un type de comitial, c'est-á-dire qu'il n'est pas seulement un psychopathe de naissance, mais vraiment un malade.[8]

Concluding, they state:

> Mais lorsque nous avons proposé le mal comitial comme condition déterminante de ce drame, nous avons évidemment risqué une hypothése. Cependant l'obnubilation crépusculaire du début, les hallucinations visuelles accompagnant la phase excitomotrice, l'amnésie totale postconfusionelle, la dépression finale, voilá bien un syndrome qui nous donne quelques raisons de penser que sans doute l'observatione et sûrement la imagination creatrice de Sophocle ne sont pas en opposition formelle avec les faits cliniques modernes et leurs interprétations actuelles concernant les états confusionnels excitomoteurs épileptiques. Nous avons cru méme voir dans l'issue de ce drame la resultante des réactions d'un fonds mental psychopathique á l'une de ces crises comitiales.[9]

Thus, we see that several competent scholars have examined the behaviour of Orestes, Heracles, and Ajax, and have concluded that certain of their actions indicate that they suffered from epilepsy. Do we have any evidence that Philoctetes, too, suffered from this disease?

Let us begin our study by listing some of the most noticeable features of the attack experienced by Philoctetes, as we find them set forth in lines 730–894.[10]

1. Philoctetes, who has been walking and conversing with Neoptolemus stops, and a change comes over his countenance.[11]

[3] Owsei Temkin: *The Falling Sickness* (Baltimore, 1945), p. 17.

[4] Ainsworth O'Brien-Moore: *Madness in Ancient Literature* (Weimar, 1924).

[5] *Ibid.*, p. 122.

[6] *Ibid.*, p. 122.

[7] *Ibid.*, p. 144.

[8] B. Pommé and Ph. Scouras: "L'Epilepsie dans Sophocle," *Aesculape*, 1932, p. 123.

[9] *Ibid.*, p. 127.

[10] Sophocles: *The Philoctetes*. ls. 730–894.

[11] *Ibid.*, ls. 730–731.

2. He groans and calls upon the gods for help.[12]

3. Again he cries aloud, and then begs Neoptolemus to ease the pain in his heel by shearing it off with his sword.[13]

4. The sufferer indicates that he knows the course which the attack will follow and tells Neoptolemus that he must soon fall into a deep sleep.[14]

5. He beseeches Neoptolemus to put an end to his wretched life by seizing him and throwing him into the Lemnian volcano.[15]

6. Just as he entreats Neoptolemus to take him to his cave and to remain with him during the attack, Philoctetes' speech and manner show a new frenzy and his rolling eyes are upturned to the sky.[16]

7. Dropping to the ground, his head sinks backwards, and bathed in a sweat, he becomes unconscious.[17]

8. After a period of time during which he is completely insensible, the Malian warrior awakes feeling faint, and is helped to his feet by Neoptolemus.[18]

In addition, are there any references to the frequency of occurrence of the attacks or to their seriousness? In line 758, Philoctetes states *ἥκει γὰρ αὕτη διὰ χρόνου, πλάνοις ἴσως ὡς ἐξεπλήσθη.*[19] Sir Richard Jebb declares that *ἥκει* is an example of a "gnomic" perfect,[20] thus indicating that the attack is definitely a repeated occurrence.

διὰ χρόνου, "after an interval of time," implies that the period between these attacks is a considerable one. *πλάνοις* indicates that the periods between attacks were irregular. Jebb says that the word was suggested by the fact that intermittent fevers were called *πλάνητες*. In lines 807–8, Philoctetes tells Neoptolemus *ὡς ἥδε μοι ὀξεῖα φοιτᾷ καὶ ταχεῖ' ἀπέρχεται.*[21] Although the periodic attacks are severe, they last but a little while and are gone. Throughout the play, there are a number of references to the severity of the disease (*ἡ ἄγρια νόσος*) with which Philoctetes was vexed.[22] Lines 258–259 *ἡ δ' ἐμὴ νόσος ἀεὶ τέθηλε κἀπὶ μεῖζον ἕρχεται,*[23] mean that the disease had been increasing in its severity. Thus Philoctetes is the victim of seizures which neither occur frequently, nor with regularity, nor are of great duration when they do strike him. Yet they had been becoming increasingly more severe.

Just how well does this picture fit in with what we now know about epileptic seizures? The symptoms for the most part are typical of the grand mal variety of epileptic seizure. This type is characterized by an aura, a convulsion, and a post-convulsive state.[24] The aura is usually the first indication of the impending seizure and may consist of "momentary subjective feelings or even objective motor and vasomotor phenomena. . . ."[25] The convulsion, often beginning with a shrill cry, usually follows the aura either immediately or after a lapse of several seconds or minutes. There is first a tonic phase in which the entire body becomes rigid and both the arms and legs are extended. This lasts for as long as a half minute and then there follows the clonic phase during which "the spasm becomes interrupted by vibrations which become less frequent and more pronounced, with more complete intermissions."[26] When the vibrations cease there occurs the postconvulsive state, in which the victim may fall into a deep sleep of up to several hours in length. From this he may awaken quite clear of mind or in a state of confusion.

[12] *Ibid.*, ls. 732–739.
[13] *Ibid.*, ls. 742–750.
[14] *Ibid.*, ls. 763–769.
[15] *Ibid.*, ls. 799–800.
[16] *Ibid.*, ls. 814–817.
[17] *Ibid.*, ls. 819–822.
[18] *Ibid.*, ls. 865 ff.
[19] *Ibid.*, ls. 758–759.
[20] Sir Richard C. Jebb, *Sophocles: The Philoctetes* (London, 1932), p. 124.
[21] Sophocles: *op. cit.*, ls. 807–8.
[22] *Ibid.*, ls. 172–3, ls. 311–313, etc.
[23] *Ibid.*, ls. 258–259.
[24] Bernard J. Alpers: *Clinical Neurology*, (Philadelphia, 1958) p. 630.
[25] Israel S. Wechsler: *A Textbook of Clinical Neurology*, ed. 8, (Philadelphia and London, 1958), p. 592.
[26] Roy R. Grinker and Paul C. Bucy: *Neurology* (Springfield, Ill., 1949), p. 854.

We noticed that a change occurred in Philoctetes' appearance and that this was followed by a sensation of pain in his foot. The change in appearance could certainly be considered to be part of the aura, perhaps caused by a subjective feeling of strangeness or unreality, or perhaps by an unusual depression or elation of spirits. In fact, there are any number of sensory or psychic auras which might have been responsible for the change in appearance. The feeling of pain experienced by Philoctetes could also be part of the epileptic aura.[27, 28] The aura or warning may be so distinct and of such duration as to enable the victim to lie down or seek a place of safety.[29] Philoctetes, realizing that a seizure was imminent and that he would shortly undergo a period of unconsciousness, made arrangements with Neoptolemus for the care of his bow, and then, before lapsing into an insensate state, pled with Neoptolemus to take him to his cave where he would be able to lie on his bed of leaves.[30]

At this stage of an epileptic attack, morbid and sudden impulses are not uncommon, sometimes approaching distinct nerve storms.[31] Possibly Philoctetes' desire to have Neoptolemus shear off his heel with a sword and his later request to be thrown into the Lemnian volcano may be understood as such.

It is possible that the prolonged cry of Philoctetes is merely that of a man in pain, or, save for the fact that it does not occur just at the time of loss of consciousness, it may be the wild, harsh, screaming sound that often precedes the more serious form of an epileptic attack. The latter type of vocalization is caused by the spasm of the thoracic and abdominal muscles expelling air through the narrowed glottis.[32] Perhaps giving strength to this interpretation, Jebb notes that the cries, as we find them written in line 746,[33] "suggest the convulsive movement of the lips from which the sounds are rung."[34]

Philoctetes next exhibits some of the more pronounced signs of an epileptic attack. As a frenzy seizes him, his eyes roll upward, he falls helplessly to the ground, loses consciousness, and is bathed in a sweat. Each of these manifestations is quite typical of the convulsive stage of the grand mal epileptic attack.[35] It appears that Philoctetes lapsed into a deep sleep such as that which characterizes the post convulsive state. He returns to consciousness feeling faint and exhausted, but with clarity of mind.

After awakening, Philoctetes stated that the attack had allowed him "a space of forgetfulness."[36] This is in keeping with Harrison's statement that the grand mal victim "is completely unaware of what has happened or at most remembers only the aura. He may come to his senses . . . and his only way of telling that something has happened is by the hiatus in his memory. . . ."[37]

Neoptolemus told the awakened Philoctetes that he was glad to see him living and breathing for his symptoms had "seemed to speak of death."[38] Graves declares that these "symptoms" or *συμβόλαιά* referred to the hue of Philoctetes' skin and to "his apparent cessation of breathing" at one point in the attack.[39] That such findings are typical of a grand mal attack is evidenced by Harrison when he declares that "With continued spasm of the respiratory muscles breathing is impossible, and the color of the skin and mucous membranes becomes dusky or cyanotic."[40]

Attacks of this sort succeed one another with varying frequencies and regularities. Some

[27] *Ibid.*, p. 852.

[28] Wechsler: *op. cit.*, p. 592.

[29] Alpers; *op. cit.*, p. 631.

[30] Sophocles: *op. cit.*, ls. 763 ff., 814.

[31] William P. Spratling: *Epilepsy and its Treatment* (Philadelphia, New York and London, 1904), p. 214.

[32] Grinker and Bucy: *op. cit.*, p. 853.

[33] Sophocles: *op. cit.*, l. 746.

[34] Jebb: *op. cit.*, p. 123.

[35] Alpers: *op. cit.*, p. 632.

[36] Sophocles: *op. cit.*, ls. 877–878.

[37] T. R. Harrison: *Principles of Internal Medicine* (New York, Toronto, London, 1958), p. 324.

[38] Sophocles, *op. cit.*, ls. 884–885.

[39] Frank Pierrepont Graves: *The Philoctetes of Sophocles* (Boston, Chicago, 1893), p. 182.

[40] Harrison, *op. cit.*, p. 324.

epileptic seizures are separated by periods of several years, whereas in other cases the attacks occur several times a week or almost daily.[41] In some instances the seizures happen with clock-like regularity, but in most there is no predictable pattern. The picture that we have of wide intervals between attacks which take place with no regularity, certainly does not present a pattern which is unusual.

If we wish to go further, there are other elements in the story that Sophocles has given us which may be shown to be in harmony with the concept of an epileptic Philoctetes.

The attitude of the Greek chieftains toward the young warrior from Malis may be easily explained if we recognize that the cries which filled the sanctuary of Chryse were those of a victim of the "falling sickness." "To the ancients the epileptic was an object of horror and disgust, and not a saint or prophet as has sometimes been contended."[42] Generally, the epileptic was detested, abhorred, and shunned. Since he was an unclean person, "taboo" particularly during his attack, we may realize something of the horror and concern the Greeks might have felt when the sacrifice at Chryse's altar was interrupted by the cries of Philoctetes. Shortly thereafter, the chiefs sailed to the Isle of Lemnos and left the sufferer there, while the fleet sailed on to Troy.[43] Also, the view that the Malian warrior was an epileptic may easily explain the anxiety felt by him lest Neoptolemus forsake him at the sight of his disease.[44]

The alleged divine origin of the Malian warrior's affliction and his cure by Asclepius perhaps deserve mention. Neoptolemus reveals in line 1326[45] that Philoctetes' trouble had been ordained by the gods. This notion had probably long been common, for Hippocrates, about 400 B.C. attacked the prevalent assumption that the gods were the cause of epilepsy. Temkin suggests that even the name "sacred disease" came about because of the belief that a deity had sent it.[46]

Sophocles reveals that Asclepius would heal Philoctetes. There is no evidence that Asclepius or his sons, Podalirius and Machaon, were credited with being able to heal epilepsy in the period of the Trojan War, though later testimonies definitely claim that the healing god could cure the affliction.[47] The patient seeking the help of Asclepius would sleep in the temple where the god would appear to him in a dream to effect or advise a cure.[48]

Having looked at the illness of Philoctetes in the light of modern medical knowledge and having made allowance for poetic license, we may conclude that Sophocles has depicted a sickness which closely resembles grand mal epilepsy, and that this was probably either an attempt by the playwright to make the illness more awesome and thereby heighten the dramatic effect, or it was an actual reflection of an epileptic attack which came upon the Greek warrior Philoctetes at the commencement of the war against Troy.

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[41] *Ibid.* p. 649.

[42] Temkin: *op. cit.*, p. 8.

[43] Sophocles: *op. cit.*, ls. 268–270.

[44] *Ibid.*, l. 789.

[45] *Ibid.*, l. 1326.

[46] Temkin: *op. cit.*, p. 6.

[47] *Ibid.*, p. 14. "NN. from Argos, epileptic. This man during his sleep in the curative chamber saw a vision: he dreamed that the god approached him and pressed his ring . . . upon his mouth, nostrils and ears—and he recovered."

[48] Temkin: *op. cit.*, p. 14.

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A Student's Note Book from William Osler's Clinics in Philadelphia[1]

By SAMUEL X RADBILL, M.D.[2]

FORTUNE is a lovely lady! One afternoon, while waiting in the office of my friend, Dr. Herman Ostrum, I happened to mention to his affable secretary, Miss Ernestine Mercer, my penchant for *Osleriana*. "My father, Dr. Charles Price Mercer, was one of Osler's students," she said. "I still have his student note books at home."

Dr. Joseph H. Pratt, in 1949, published his notes taken when he was a student in 1896 and 1897 at Osler's clinics at the Johns Hopkins Hospital, and an analysis of Osler's prescripions was written by Dr. David I. Macht some time ago. But I had no recollection of ever seeing a student note book from Osler's clinics during his Philadelphia days. To my great joy, a few days later, Miss Mercer presented me with her father's note book.

Charles Price Mercer was born in Philadelphia on October 2, 1864. He spent his entire life in this city. After college preparatory study at the Lauterbach Academy, he proceeded to the University of Pennsylvania, there to earn the degree of Ph.B. in 1886. He then enrolled in the medical course, taking his M.D. in 1891. The University of Pennsylvania had just instituted the three-year course of study in the School of Medicine then, with a fourth year optional. The preceptor system was still technically in vogue and Dr. S. T. Newber was listed as Mercer's preceptor.

Dr. Mercer began to practice medicine on December 4, 1891. A few weeks later he was appointed vaccinating physician for the Board of Health. In 1893, the Board appointed him a medical inspector, and he served in the Philadelphia Health Department until 1931.

When he married, in 1895, he moved to 2554 North Eighth Street and continued in general practice there until his death on September 19, 1945.

"What bare bones a *vita* can be!", says Miss Mercer. "Nothing about my father's feeling for language—something not too common among doctors, as you no doubt will agree, nothing about his travels, his skittish Hambletonians, his medal for winning the mile at Penn on one occasion (he was a member of the track team in his undergraduate days), though George Wharton Pepper usually beat him." In 1918 he became a member of the Voluntary Medical Service Corps, but since he never did anything for them but wear a button—he never considered it much of an accomplishment."

In 1876 the University of Pennsylvania moved from Ninth and Market Streets to its present location in West Philadelphia. Medical Hall (now Logan Hall), at the corner of 36th and Spruce Streets, directly across the way from the proud new University Hospital, was the headquarters building of the Medical School until the present Medical Laboratories Building on Hamilton Walk was opened in 1910. When Mercer was a medical student, Dr. William Pepper was provost of the University; several years before he had stepped into the position vacated by Alfred Stillé as Professor of Medicine, vacating the Chair of Clinical Medicine to William Osler.

The winter session of the Medical School began on October first. The first year student, in addition to his studies in chemistry, pharmacy, osteology, histology, physiology and dissection, was permitted to attend clinical lectures in general medicine and general surgery. At one o'clock in the afternoon, Dr. Osler met his section of the class of third year students in the University Hospital.

[1] Read before the Section on Medical History, College of Physicians of Philadelphia, 18 April 1961.

[2] Past Chairman, Section on Medical History.

Mercer also attended Dr. Pepper's clinics. William Pepper was head of the Medical Department, had a large general practice, was busily engaged in many educational and civic activities, and so had little time to come to the hospital wards. Therefore, Osler, devoted to full time teaching and research, had the wards largely to himself. The contrast between Pepper and Osler must have been striking to the students. Osler was only thirty-five years of age when he came to Philadelphia in October 1884, a comparatively young and little-known stranger. At first his students were disappointed. "No polished declamations with glowing word pictures of diseases, such as they had listened to from Stillé and Pepper, and for which the Philadelphia school was then famed, came from this swarthy person with drooping mustache and informal ways, who, instead of arriving in his carriage, jumped off a street car, carrying a small black satchel containing his lunch, and with a bundle of books under his arm; who was more apt to pop in by the back door instead of by the main entrance; who wore a frock-coat, top hat and a flowing red neck-tie, low shoes and heavy worsted socks which gave him a foreign look; who, far from having the eloquence of his predecessors, was distinctly halting in speech; who always insisted on having actual examples to illustrate his lectures, and, likely as not, sat on the edge of the table swinging his feet and twisting his ear instead of behaving like an orator—this, at least, was not the professor they had expected." (Cushing's Life", *1*: 234).

His first ward class, however, was an eye-opener, for the bedside instruction which he was accustomed to give was an undeveloped feature in the Philadelphia school. It is difficult for us to realize that at that time not only were there no laboratories, but the only microscope in the University Hospital was Osler's. Almost within a month of his arrival, he and Dr. George Dock contributed from their own pockets to equip a small clinical laboratory, and Osler had probably the first blood corpuscle counting apparatus in Philadelphia. In Mercer's notes we find blood counts noted several times.

Having no office hours or rounds of house calls, he was able to go, many afternoons, with a group of students to the "dead-house" to perform post-mortem examinations. In 1885, about a year after his arrival in Philadelphia he obtained an appointment to the medical staff of the Philadelphia (General) Hospital, then referred to as "Blockley". Although a microscopist had been appointed to this hospital in 1866, and a pathologist in 1871, it was not until Osler's time, 1885–86, that a small two-story building was erected for a laboratory and morgue. Here Osler performed 162 autopsies; this quaint building is now preserved as the Osler Memorial Museum, a "shrine to ambition and hard work", thanks to the unceasing efforts of Drs. Robert J. Hunter and Abraham Cohen.

In 1885, Osler was also appointed attending physician to the Orthopedic Hospital and Infirmary for Nervous Diseases, and frequently herded his students there, particularly to study the nervous conditions of children. Aided by Dr. Charles W. Burr, who was then a resident physician in the hospital, he prepared for publication his clinical lectures of 1888 on "The Cerebral Palsies of Children". The new building of the Philadelphia Orthopedic Hospital had been opened in March 1887, only a few months before Charles P. Mercer began his medical studies; his notes record cases presented to the class there.

William Osler was gifted with a love and talent for teaching. He kept abreast of the latest medical information and he knew how to teach what he knew. All his teaching was done at the bedside, the bed being wheeled into the lecture room before the class, or a group of students clustered around him as he went from one patient to the other on the wards. He endeavored to teach the medical student how to observe, record and analyze. He believed "it is a safe rule to have no teaching without a patient for a test." Pneumonia, typhoid and tuberculosis were prevalent diseases, the protean nature of which he hammered incessantly

into his students. As cases were presented, emphasis was placed on demonstrating methods of examination and indications for treatment. Osler always related the signs and symptoms to the underlying organ pathology as found in the post-room. There is little hint in Mercer's note book of the intense research activity going on at the time in bacteriology, hematology and so on. Only sketchy definitive knowledge was presented, no doubt to simplify the presentation to the medical students. Considered by his contemporaries a therapeutic nihilist, one of Osler's reliable prescriptions was "time in divided doses." It was said of him that his favorite therapy consisted of "Hope and Nux Vomica".

At the time the tyro Mercer was attending these clinics and diligently taking down his notes as best he could, Osler was busily engaged in his clinical teaching, in laboratory and post-mortem studies, attending meetings and forever writing. He lectured to his students in the wards of the University Hospital, Blockley, and the Infirmary for Nervous Diseases.

On June 1, 1888, Mercer records in his diary that he visited the Elwyn School with Dr. Osler. There in Delaware County, Pennsylvania, just south of Media and about 15 miles from the University, is the Pennsylvania Training School for Feebleminded Children, originally founded as the Pennsylvania Training School in Philadelphia in 1853, where Séguin, a political refugee from France, first tried to develop a private school for mentally defective children. Osler was a pioneer in America in the study of cretinism at a time when thyroid extract was just coming into use. At Elwyn, Dr. Kerlin was able to show him and the twenty students from the University who accompanied him, many Mongolian idiots and teach them the differentiation of this disease from congenital hypothyroidism, or "sporadic cretinism", as Osler called it.

In the spring of 1886, Osler listened to Councilman report on the malarial organisms which Laveran had discovered six years earlier. Osler at that time thought they were only cellular vacuoles, but he was busy with his microscope studying the blood of malarial patients at Blockley. Drawings he made of these organisms, still preserved at the Philadelphia General Hospital, were exhibited not so long ago by Robert J. Hunter. Continuing these studies assiduously, by the following autumn he was convinced of Laveran's correct interpretation of the significance of these parasites. So we find in the first case of malaria noted in Mercer's student note book that Osler was relying upon the demonstration of the malarial organism to make his diagnosis. Four cases were brought before the class and a description given of the organisms in different stages. Later, obscure cases of malaria were again presented with a discussion of the differential diagnosis. Quinine was the specific drug treatment.

The first clinic in the note book was devoted to the stomach—one case with a tumor; another, "gastralgia", which might have been gallstone colic or peptic ulcer. Although Osler knew about the test breakfast introduced by Ewald and Boas in 1885, our student does not mention it in his notes.

The next session was devoted to typhoid fever; in May, ambulatory typhoid was presented; in September and October we find typhoid again before the class. Osler told how to distinguish typhoid fever from "galloping consumption". Mercer does not note bacteriology, however, although bacteriological studies were introduced in this country almost a decade previously by Welch, Prudden, Sternberg and others. The bacillus of Eberth had been discovered in 1880, Koch's bacillus in 1882, and Pepper told Mercer and his fellow students to look for the bacillus of tuberculosis in cases of consumption shown at his clinics running concomitantly with Osler's. In his text-book, which first appeared in print in 1892, Osler specifically stated that the typhoid bacillus is constantly associated with typhoid fever and he recognized drinking water as its most common vehicle. As for tuberculosis, in his book, Osler acknowledged

the bacillus of Koch as the essential element, its presence in the sputum being an infallible indication of the disease.

Osler makes frequent mention of the arterial tension in cardiovascular diseases but, of course, there is no mention of actual recordings of the blood pressure. Although Von Basch had invented a sphygmomanometer in 1878, and later Potain had improved on the cumbersome instrument, general use of it had to await the work of Janeway early in our own century.

Bright's disease with urinary findings, gonorrheal rheumatism, endocarditis—acute and chronic, aortic aneurysm, angina pectoris, the complications of pneumonia, brain abscess in a case of which eye ground findings are noted, infantile hemiplegia (including the various types of cerebral palsy), poliomyelitis, meningitis, encephalitis, hemorrhage from a gastric ulcer in which the red corpuscle count dropped to 800,000, ascites, etc., all received their share of attention as patient after patient paraded before the class. Patients were often brought back at subsequent lectures for follow-up; when death occurred, the pathological specimens were brought before the students and carefully studied to correlate the post-mortem findings with the previous clinical findings.

In October, 1888, Osler accepted the professorial appointment to Johns Hopkins University. On December 20, 1888, Dr. Judson Daland, one of his clinical assistants, lectured to the class in his place; and on January 19, 1889, it was another assistant, John H. Musser *vice* Osler. On the morning of May 1, 1889, at the close of the course, Osler presented his farewell address to his Pennsylvania students, one of the best he ever gave—"Aequanimitas". This address should still be read by every doctor embarking upon the rough seas of medical practice.

Transactions of the Section on General Medicine

27 February 1961

Loeffler's Syndrome Associated with Nickel Sensitivity. F. William Sunderman, M.D., Ph.D., and F. William Sunderman, Jr., M.D. (Discusser: Joseph V. Klauder, M.D.) (*Abstract 1*, below)

Ineffective Erythropoiesis. Farid I. Haurani, M.D.* (Discusser: Leandro M. Tocantins, M.D.) (*Abstract 2*, below)

The Syndrome of Primary Hypoaldosteronism. James E. Clark, M.D.* (Discusser: George R. Fisher, III, M.D.*) (*Abstract 3*, below)

A Comparative Evaluation of Renal Function Tests. Leonard S. Dreifus, M.D.*, Cristobal Duarte, M.D.*, Albert N. Brest, M.D.*, Joseph Rosenfeld, M.D.*, and John H. Moyer, M.D. (Discusser: Earl S. Barker, M.D.) (*Abstract 4*, below)

27 March 1961

Some Clinical and Experimental Applications of Cineradiography (with motion picture). Herbert M. Stauffer, M.D. (*Abstract 5*, below)

Cineradiography of the Upper Gastrointestinal Tract (with motion picture). Henry J. Woloshin, M.D.* (Discusser: Theodore A. Tristan, M.D.*) (*Abstract 6*, below)

Salmonellosis Due to Contaminated Fish: Report of One Fatal and One Recovered Case. William S. Frankl, M.D.*, and Fred B. Rogers, M.D. (Discusser: John J. Hanlon, M.D.) (*Abstract 7*, below)

Macroglobulinemia. Warren D. Davidson, M.D.* (Discusser: Howard M. Rawnsley, M.D.*) (*Abstract 8*, below)

24 April 1961

Hemodynamic Actions of Guanethidine. Albert N. Brest, M.D.*, Paul Novack, M.D.*, and John H. Moyer, M.D. (Discusser: Louis A. Soloff, M.D.) (*Abstract 9*, below)

Recognition of Right Auricular Thrombosis by Negative Contrast Roentgenography. Jacob Zatuchni, M.D., and Richard B. D. Chun, M.D.* (Discusser: Thomas M. Durant, M.D.) (*Abstract 10*, below)

Leucine-Induced Hypoglycemia: Speculation on Pathogenesis. Angelo M. DiGeorge, M.D.*, Victor H. Auerbach, Ph.D.*, and C. Charlton Mabry, M.D.* (Discusser: Robert Kaye, M.D.*) (*Abstract 11*, below)

Studies of Thyroxine Analogues, with Comments Concerning Their Use in Patients with Cardiovascular Diseases. Marvin L. Sachs, M.D.* (Discusser: Norman G. Schneeberg, M.D.*) (*Abstract 12*, below)

Abstract 1

Loeffler's Syndrome Associated with Nickel Sensitivity. F. William Sunderman, M.D., Ph.D., and F. William Sunderman, Jr., M.D., Jefferson Medical College of Philadelphia.

A case is reported of a 52-year-old, white male chemical engineer who developed asthma and Loeffler's syndrome associated with exposure to the vapors of nickel carbonyl. In addition to pulmonary infiltrations and eosinophilia, typical of Loeffler's syndrome, the patient exhibited an eczematous dermatitis of the hands. Patch testing demonstrated extreme sensitivity to nickel. Bed rest and withdrawal from all contact with nickel resulted in relief of symptoms and disappearance of the lesions. This case represents the second reported instance of an association between Loeffler's syndrome and nickel sensitivity.

Abstract 2

Ineffective Erythropoiesis. Farid I. Haurani, M.D., Assistant Member, and Leandro M. Tocantins, M.D., Director, Charlotte Drake Cardeza Foundation, Jefferson Medical College of Philadelphia.

The term "ineffective erythropoiesis" was

* By invitation.

introduced (1) to describe hematologic disorders in which there is a discrepancy between the total hemoglobin mass in the peripheral circulation (effective erythropoiesis) and heme synthesis in the bone marrow (total erythropoiesis) unexplained by blood loss alone (hemolysis or hemorrhage). In this state, though total erythropoiesis may be increased many times the normal, most of the synthetized heme seems to be destroyed in situ and is not destined to reach the peripheral circulation or else it survives very shortly (hours) in the peripheral circulation (2). This study is concerned with diseases in which various degrees of ineffective erythropoiesis were manifested and with a comparison of the results with those obtained in other diagnostically closely related disorders in the same group. Among the six indices, the reticulocyte, red cell utilization and Cr^{51} survival represent effective erythropoiesis while plasma iron turnover, fecal urobilinogen and bone marrow cell composition represent total erythropoiesis. For analysis the results were arranged in four groups.

Group 1. Hemoglobinopathies: Thalassemia major, strictly speaking not a hemoglobinopathy, was included to provide a basis for comparison. Erythrokinetic studies in this group revealed ineffective erythropoiesis only in patients with thalassemia major. In the three patients with sickle-thalassemia and one patient with Hemoglobin I-thalassemia a decrease in effective erythropoiesis could not be demonstrated.

Group 2. Myelosclerosis and extramedullary hemopoiesis: This group consists of ten patients with extramedullary hemopoiesis and two with chronic myelogenous leukemia. The total erythropoiesis of these extramedullary foci is not remarkably higher than normal as compared to thalassemia, sickle cell anemia or megaloblastic anemia. Ineffective erythropoiesis does exist in these extramedullary foci. In the two patients with chronic myelogenous leukemia, ineffective erythropoiesis was not demonstrated. The anemia seems to be secondary to a relative bone marrow failure.

Group 3. Refractory anemia. This group consists of 8 patients. Five had aplastic anemia and three had refractory normoblastic anemia. Ineffective erythropoiesis was demonstrated in the patients with refractory normoblastic anemia of the group. The total erythropoiesis was about 5 × normal; however, the effective erythropoiesis was poor, giving the bone marrow an efficiency of 15 to 30%. In contrast, patients with aplastic anemia have a poor total erythropoiesis and, as a result of this, the effective erythropoiesis is poor too.

Group 4. Miscellaneous. This last group consists of six patients. Two had hemochromatosis and had almost normal erythrokinetic studies except for the plasma iron turnover and the Fe^{59} utilization production indices. The next three patients had a megaloblastic anemia due to malabsorption of vitamin B12, acute di Guglielmo disease and polycythemia vera, respectively. Total erythropoiesis was increased markedly in megaloblastic anemia and di Guglielmo disease as compared to the patient with polycythemia vera where total erythropoiesis was slightly more than normal. Because of the ineffective erythropoiesis in megaloblastic and di Guglielmo disease, the patients had an anemia, whereas in polycythemia vera, where the efficiency of the bone marrow is normal, the patient had erythrocytosis.

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Abstract 3

The Syndrome of Primary Hypoaldosteronism. James E. Clark, M.D., Department of Medicine, Jefferson Medical College of Philadelphia.

The syndrome of primary hypoaldoster-

onism may appear in either of two clinical forms. Patients may manifest either potassium retention with hyperkalemia and electrocardiographic changes, or severe sodium wasting, hyponatremia, weakness and muscle cramps. Two patients have been studied, one in detail, representing each of the clinical varients.

One patient, a sodium loser, was hospitalized with fever, dehydration, extreme weakness, muscle cramps and severe hyponatremia. She was excreting no detectable quantities of aldosterone in 24-hour urine collections. Sodium replacement or treatment with DOCA corrected her electrolyte abnormalities, and resulted in disappearance of her symptoms. The second patient displayed recurrent episodes of hyperkalemia associated with intermittent electrocardiographic changes of wide QRS complexes. Intravenous infusion of potassium reproduced the electrocardiographic changes. The serum potassium and ECG changes were controlled with sodium replacement or treatment with DOCA. No detectable aldosterone was found in 24-hour urine collections, and after sodium depletion, only minimal amounts were present. Aldosterone excretion from the adrenals was estimated using tritium labeled aldosterone. These values were abnormally low, and rose only minimally after sodium deprivation. Adrenal function was otherwise normal in both patients in respect to glucocorticoid excretion, as determined by urine and plasma levels before and after ACTH stimulation. No roentgenographic evidence of an adrenal tumor was found. Both patients are believed to represent selective aldosterone deficiency of the adrenal glands. Whether the defect lies primarily in the adrenals, or somewhere in the receptor pathway mechanism is unknown.

Abstract 4

A Comparative Evaluation of Renal Function Tests.* Leonard S. Dreifus, M.D., Associate in Medicine; Cristobal Duarte, M.D., Fellow in Renal Disease; Albert Brest, M.D., Director, Hypertension and Renology Sections; Joseph Rosenfeld, M.D., Fellow in Renal Disease; and John H. Moyer, M.D., Professor and Chairman of the Department of Medicine, Hahnemann Medical College.

Since the usual course of renal disease involves both filtration as well as concentrating mechanisms (1) it may be sufficient that a single test of tubular concentration would adequately evaluate renal function in health and disease.

Eighty hypertensive patients without clinical evidence of renal disease and ten normal subjects were evaluated by maximum osmolar concentration, inulin, PAH, creatinine, total solute, and free water (C_{H_2O}) clearance studies. In addition, the maximum free water reabsorption ($T^c_{mH_2O}$) was determined under an osmotic mannitol diuresis in another five patients.

Although there was a fairly good correlation between urine specific gravity and maximum osmolal concentration, frequent discrepancies were noted. A majority (82%) of these hypertensive patients could not elaborate urine osmolal concentrations greater than 740 mOsm/Kg. (2).

In the specific gravity range of 1.010 to 1.014, usually interpreted as a loss of renal concentrating ability, urine osmolal concentration sometimes exceeded 740 mOsm/Kg. On the other hand, urine osmolal concentrations of 740 mOsm/Kg or less were at times associated with a specific gravity of 1.020 or more.

A rather close correlation existed between glomerular and concentrating function (Table 1). The mean inulin clearance in the hypertensive patients was 73 ± 4.9 ml/min., creatinine clearance 79 ± 1.8 ml/min., maximum free water reabsorption 1.89 ± 1.1 and maximum osmolar concentration 640 ± 104 mOsm/Kg.

As $T^c_{H_2O}$ approaches a constant value ($T^c_{mH_2O}$) under a non-reabsorbable solute diuresis, the renal tubules are demonstrating their maximum reabsorptive ability. This is

* This study was supported by the Southeastern Pennsylvania Heart Association and National Institutes of Health Grant H 3511.

TABLE 1

COMPARISON OF GLOMERULAR FILTRATION AND TUBULAR FUNCTION

	Normal Subjects	Hypertensive Patients
Inulin clearance	100–120 ml/min.	Δ, 73 ± 4.9 ml/min.
Creatinine clearance	100–160 ml/min.	Δ, 79 ± 1.8 ml/min.
Maximum urine osmolar concentration	Δ, 1076 ± 96.8 ml/min.	Δ, 640 ± 104 ml/min.
Maximum free water reabsorption $\left(T^{c}_{m\,H_2O}\right)$	Δ, 5.0 ± 1.0 ml/min.	Δ, 1.89 ± 1.1 ml/min.

Δ Standard error of the mean.

probably the best judge of renal concentrating ability (3, 4). In these studies, maximum urinary osmolar concentration agreed favorably with the $T^{c}_{mH_2O}$ and GFR of hypertensive patients and hence may serve as an adequate, early, accurate, and sensitive evaluation of renal function. Abnormalities of glomerular and concentrating function will still require elaborate study in an attempt to understand specific pathophysiological mechanisms.

Finally, there appears to be an early defect in renal concentrating ability of hypertensive patients, even though ordinary tests of renal function appear normal.

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Abstract 5

SOME CLINICAL AND EXPERIMENTAL APPLICATIONS OF CINERADIOGRAPHY. Herbert M. Stauffer, M.D., Professor of Radiology, Temple University School of Medicine.

Clinical cineradiography has become practical since the introduction about ten years ago of electronic fluoroscopic image intensifiers. The x-ray motion picture technique is particularly valuable where motions are too rapid or too complex to be analyzed by conventional fluoroscopy or a succession of conventional x-ray films. The swallowing act and heart action are good examples of such motions which can only be well analyzed by cineradiography. The motility of the gastrointestinal tract, of the urinary tract and joint motions are also important areas of application of this method.

In both clinical and experimental applications a useful modification of the technique is the simultaneous recording of other physiologic data simultaneously on the movie film showing structural behavior revealed radiographically. For instance, recordings of voice and heart sounds, of the ECG and pressure pulses and of pressure changes within the gastrointestinal tract can be recorded simultaneously on the movie film for subsequent analysis and correlation.

Several experimental studies in animals have been carried out in the laboratories of Temple University School of Medicine, representing cooperative efforts of members of the Departments of Radiology, Physiology, Medicine and Medical Physics.

Cineradiographic studies of dogs at 60 frames per second showed the rapid dispersal of large quantities of intravenously injected carbon dioxide and the safety of this technique for radiographic visualization of the interior of the heart. Considerable clinical application of this method in the study of pericardial abnormali-

ties over the right heart border has developed on the basis of these experimental studies (1). Cinefluorographic study at 60 frames per second in dogs demonstrated regurgitation of opaque contrast material through the normal mitral valve when injected into the left ventricle during or immediately preceding a period of prolonged diastasis. Appreciation of this phenomenon may prevent misinterpretation of such transient mitral regurgitation accompanying arrhythmia or asystole during left ventriculography (2).

Cinefluorographic studies at 60 frames per second during selective intracoronary injection of small doses of angiographic radio-opaque media have shown a specific toxic action of Urokon with extra vascular diffusion of the contrast material and hemorrhagic myocardial necrosis (3).

One laboratory is now specially equipped for the study of vascular flow patterns with x-ray movies made of the intact animal at 250 frames per second. The analysis of the resulting films is facilitated by partially automated electronic equipment providing velocity or acceleration information as desired. Caval flow patterns, indicated by droplets of opaque oil, were different in the superior and the inferior cava in tachycardia. In the superior vena cava, the droplets move toward the heart during systole but stop or move retrograde during diastole, while in the inferior vena cava, under similar conditions, the droplets move forward both during systole and diastole. In bradycardia the flow patterns in the superior and inferior vena cava are more nearly alike (4).

Preliminary studies using a similar technique with opaque droplets in the aorta have shown dramatic differences in the pattern of acceleration and deceleration after induced myocardial infarction.

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Abstract 6

Cineradiography of the Upper Gastrointestinal Tract. Henry J. Woloshin, M.D., Associate Professor of Radiology, Temple University School of Medicine.

Cineradiography is proving to be a valuable adjunct to the conventional roentgen study of the upper gastrointestinal tract. Our experience with more than 750 cine examinations has shown that the method adds information in situations where rapid motion is present. The motion picture film is a recording of fluoroscopic behavior and can be examined as often as desired with slow motion analysis. We obtain cine records on most of our studies of the hypopharynx and cervical esophagus. Because of the rapidity of the swallowing act, numerous radiographs are usually required for a satisfactory study. In this region, cine study is simpler and often shows extent of an organic lesion to better advantage, at the same time giving a functional record. Films are made at 30 to 60 frames per second in this region.

The esophagus and esophagogastric segment are also well suited for study by the cine method. In these areas a major advantage has been the objective and consultative study of esophageal motor behavior. Dysrhythmic activity of the esophagus is well shown. The spastic action of the distal esophagus and associated ineffectual waves above are demonstrated in cardiospasm. An appreciation of the range of variation at the esophagogastric region has come with the use of the cine method. Drug effect on esophageal motor activity has been demonstrated.

In the study of the stomach and duodenum we have found cine study useful in selected cases. These are the cases in which a suspicious finding (filling defect, fleck, large folds) has been revealed by the conventional examination. Motion picture analysis has on a number of instances clarified the problem. The method permits of study of peristalsis and the effect of palpation and rotation.

In the main, cineradiography has been supplementary to the routine study. We have not detected organic lesions which were not shown or suspected by the conventional study.

In addition to the added expense of an image intensifier tube and motion picture camera, there are a number of practical aspects to be considered before adding cineradiography to the diagnostic x-ray department. New technical problems present themselves, including those of film processing, viewing and filing. Increased x-ray exposure to the patient necessitates constant supervision. However, with judicious use, exposure can be kept well within permissible limits and in the range of other diagnostic procedures.

The potential of cineradiography is great. With increased utilization of the method it will find a more important place as a diagnostic tool.

Abstract 7

Salmonellosis Due to Contaminated Fish: Report of One Fatal and One Recovered Case. William S. Frankl, M.D., and Fred B. Rogers, M.D., Department of Medicine, Temple University School of Medicine.

We begin this presentation by quoting from Lewis Carroll. As Alice journeyed *Through the Looking Glass*, she "turned a sharp corner". There in Wonderland two figures were standing under a tree with their arms around each other's necks. Alice knew which was which in a moment, because one of them had 'dum'

embroidered on his collar, and the other, 'dee'. "I suppose they've each got 'tweedle' written on the back of their collars too", she said to herself. Shortly after this, Tweedledee recited a poem about the Walrus and the Carpenter. Among its verses were:

> " 'A loaf of bread,' the Walrus said,
> 'Is what we chiefly need:
> Pepper and vinegar besides
> Are very good indeed—
> Now, if you're ready, Oysters dear,
> We can begin to feed.'
>
> . . . . . .
>
> " 'O Oysters,' said the Carpenter,
> 'You've had a pleasant run!
> Shall we be trotting home again?'
> But answer came there none—
> And this was scarcely odd, because
> They'd eaten every one."

The two cases which we present reminded us of these two literary look-alikes and their poetic friends. Our experience with these cases was slightly less surprising, but no less interesting, than Alice's.

The first patient, B. H., a 48-year old Negro man, had invited the second patient, C. C., a 60-year old Negro man, to dinner 48 hours before they were hospitalized. They ate fish for dinner. This might have turned out pleasantly except that the fish had lain partially-cooked, but unrefrigerated in the oven, for 24 hours before ingestion. B. H.'s girl friend warned them against eating this fare, without avail. C. C. ate several forkfuls of the delicacy and then declined further morsels. B. H. ate his own portion plus that of his companion. About 5–6 hours later, B. H. began to experience weakness and mild diarrhea. C. C. noticed the same symptoms eleven hours later. This was followed in each by nausea, vomiting, tormina, and profuse, persistent, foul-smelling diarrhea. Both men became prostrate; neither was then able to ingest any liquids or solid food. Eventually, through the good office of Mr. H's girl friend, they were brought to the receiving ward of Temple University Hospital on June 27, 1960. Here they were both found to be: 1. dehydrated, 2. in moderately severe abdominal discomfort, 3. passing large, liquid, greenish-yellow stools almost continually, and 4. mentally confused and agitated.

They differed in that B. H. showed arterial hypotension (80/50), a marked tachycardia, and a rectal temperature of 105°F. They were hospitalized together, and put in beds side-by-side. A diagnosis was made of acute food poisoning, with probable superimposed Gram negative septicemia. Blood, urine, stool, sputum, and nasopharyngeal bacterial cultures were taken and the patients were given massive doses of chloramphenicol, penicillin and kanamycin, plus intravenous infusions of glucose in saline with added KCl. On saline alone, the blood pressure of B. H. rose to a near normal level. From the beginning, B. H. appeared more seriously ill and his diarrhea was more difficult to control; his BUN rose steadily and his urinary output was low. His rectal temperature did not drop below 102°F. To the fluid, electrolyte and antibiotic regimen, intramuscular gamma globulin was added for each man. Three and one half days after admission, B. H., the younger man, went into acute pulmonary edema, and despite heroic therapeutic efforts, died on July 1, 1960. By the second day after admission, *Salmonella typhimurium* (group B) was isolated from the blood and stools of B. H., and the same organism from the blood, sputum, urine, stool, and nasopharyngeal cultures of C. C. The isolated micro-organism was susceptible to both chloramphenicol and kanamycin. (The vast reservoir of salmonellae in animals constitutes a major source of salmonellosis in man. *S. typhimurium* is a natural pathogen of rodents, especially mice. Contact with rodent feces, possible through roaches, may occur in substandard housing, and usually produces an acute gastroenteritis in man.) Septicemia and osteomyelitis caused by *S. Typhimurium*, as occurred in our patients, is unusual. Autopsy of B. H. revealed gross and microscopic lymphoid hyperplasia in the Peyer's patches of the ileum and the mesenteric lymph nodes, and parenchymal congestion in the spleen, liver, and brain (Autopsy no. 60-321, performed by Dr. William A. Harada).

C. C. lived, but only after a stormy course,

which included administration of 70 liters of parenteral fluids, adrenal steroid substances to combat hypotension, and massive amounts of antibiotics following the isolation of additional staphylococcus aureus (coagulase positive) from cultures of his stools, sputum, and nasopharynx. An osteomyelitis of the head of the left humerus, of salmonella origin, and a marked acidosis with a high BUN and low urinary output coexisted. The older man finally recovered, however, and walked out of the hospital on July 23, 1960. It is interesting to note that he still had *S. typhimurium* in his stools when he left the hospital. The Philadelphia Department of Health was notified about this patient and investigated his convalescent carrier state after he returned home.

Abstract 8

MACROGLOBULINEMIA. Warren D. Davidson, M.D., Chief Resident Physician in Internal Medicine, Philadelphia General Hospital.

The syndrome of macroglobulinemia was first described by Waldenström in 1944. This entity is usually characterized by weakness, weight loss, mucosal bleeding, lymphadenopathy, hepatosplenomegaly and occasionally by decreased visual acuity. Laboratory findings include a normocytic anemia and increased numbers of plasmacytoid lymphocytes in the bone marrow. The Sia water dilution test is positive and serum protein electrophoresis reveals a tall homogeneous myeloma-type spike with a mobility close to that of gamma globulin. The diagnosis is confirmed by serum ultracentrifugation if more than 5% of the total serum protein has a sedimentation rate of 18 or more Svedberg units corresponding to a molecular weight of 1,000,000 or greater.

Recently a case of primary macroglobulinemia presenting all of the above findings was observed at the Philadelphia General Hospital. The patient was a 46-year old Negro male whose chief complaint was markedly decreased visual acuity. This symptom was found to be related to bilateral retinal vein thrombosis caused by a marked increase in the viscosity of the patient's blood due to elevated levels of macroglobulin. In an effort to remove the macroglobulins and thereby decrease the plasma viscosity, the patient was treated by plasmapheresis. This procedure involves the removal of blood into standard donor bottles, centrifugation of the specimen, decantation of the supernatant containing the abnormal macromolecule and reinfusion of the packed red blood cells. Within one week of the initiation of daily plasmapheresis visual acuity began to improve. By the third week vision returned to normal. The patient was also treated with chlorambucil because the abnormal marrow cells were predominantly lymphocytes. The patient was discharged and returned for repeat courses of plasmapheresis on two occasions. He died in shock on his last admission.

Post-mortem examination revealed splenomegaly and enlarged abdominal lymph nodes. No thrombotic or hemorrhagic lesions were noted in the general examination; however, permission for examination of the brain was not granted so a cerebral vascular accident secondary to increased plasma viscosity could not be ruled out.

It is felt that plasmapheresis is the most effective method for rapidly reducing plasma viscosity and should be considered the acute treatment of choice in any conditions exhibiting this phenomenon.

Abstract 9

HEMODYNAMIC ACTIONS OF GUANETHIDINE. Albert N. Brest, M.D., Assistant Professor of Medicine and Head, Hypertension-Renal Unit; Paul Novack, M.D., Assistant Professor of Medicine and Head, Cardiac Catheterization Laboratories; and John H. Moyer, M.D., Professor of Medicine and Chairman, Department of Internal Medicine, Hahnemann Medical College and Hospital.

The most recent therapeutic approach to hypertension includes the use of peripheral sympathetic blocking agents, especially guanethidine. This drug possesses a hypotensive potency similar to that of the ganglion blocking compounds. The blood pressure response ob-

tained is most marked with the patient in the erect position; however, in contrast with the ganglioplegic drugs, guanethidine produces an antihypertensive response without the associated side effects due to parasympathetic blockade. The antihypertensive effectiveness of the compound is further enhanced by the concomitant administration of thiazide derivatives. This new antihypertensive agent holds particular promise for those patients with the more severe degrees of diastolic blood pressure elevation.

In contrast with other drugs in the current hypotensive armamentarium, guanethidine appears to have a singular peripheral sympatholytic action. The pharmacodynamic studies of Maxwell et al. have demonstrated that guanethidine produces an inhibition of response to electric stimulation of sympathetic nerves. However, there have been no evidences of central activity or ganglionic blockade and the response to injected norepinephrine has not been reduced. It has therefore been presumed that this drug prevents the release of norepinephrine from the post-ganglionic sympathetic nerve endings.

In order to evaluate the hemodynamic response to guanethidine, the drug was administered intravenously and the acute effect on renal, cardiac, and cerebral function was assessed. The parenteral drug was administered in a dosage of 0.25 mg/kg. Renal blood flow was measured by para-amino hippurate clearance and glomerular filtration rate was determined by inulin clearance. The indicator dilution technique was used to study cardiac output, and the cerebral blood flow was measured by the Kety-Schmidt nitrous oxide method.

The cardiac hemodynamic response was determined in ten subjects. In this group, the control average mean arterial pressure fell from 163 mm Hg to 108 mm Hg, and the cardiac output fell from the control level of 5.4 liters/minute to 3.8 liters/minute. Since the changes in arterial pressure and cardiac output were in the same direction and were of similar magnitude, the calculated total peripheral resistance remained essentially unaltered.

The renal hemodynamic effect of guanethidine was studied in 8 patients. The initial, average mean arterial pressure of 135 mm Hg fell to 113 mm Hg. Accompanying the hypotensive effect, the renal plasma flow diminished from 382 cc/minute to 291 cc/minute, and the glomerular filtration rate was reduced from 94 to 79 cc/minute.

The cerebral hemodynamic response was measured in six patients. In this group, the average mean arterial blood pressure fell 36%—from 171 to 100 mm Hg. The hypotensive effect was accompanied by a 20% fall in cerebral blood flow and a similar (20%) decrease in cerebral vascular resistance. Thus the fall in blood pressure was, in part, compensated by a reduction in cerebral vascular resistance so that the percentage decline in cerebral blood flow was not so great as the fall in arterial pressure.

These hemodynamic patterns suggest that guanethidine lowers blood pressure primarily by reducing cardiac output rather than by causing an effective reduction in arteriolar tone. The fall in cardiac output could result from a direct effect upon the myocardium (possibly due to reduced tissue catecholamine levels) or else could result from a reduction in ventricular filling caused by peripheral venous pooling (venomotor blockade). Regardless of the cause, it is evident that guanethidine also depresses the reflex arteriolar constriction which usually prevents or minimizes a fall in blood pressure when cardiac output is reduced.

It is notable that the effect of guanethidine upon cardiac output, cerebral blood flow, and renal blood flow is essentially the same as that observed with ganglion blocking agents. These hemodynamic studies serve to emphasize that guanethidine must be used with caution in hypertensive patients with accompanying vascular insufficiency.

Abstract 10

Recognition of Right Auricular Thrombosis by Negative Contrast Roent-

GENOGRAPHY. Jacob Zatuchni, M.D., Clinical Professor of Medicine, Temple University School of Medicine, Teaching Chief of Medicine, Episcopal Hospital, and Richard B. D. Chun, M.D., Resident in Medicine, Episcopal Hospital.

A case is reported of a 34-year old man gravely ill with advanced coronary artery disease, persistent pulmonary emboli and peripheral thrombophlebitis. In an attempt to exclude an intracardiac thrombotic source, the technique of negative contrast roentgenography was employed because of its safety and simplicity. A thrombosed right auricle was found, and confirmed, and was manifested in the negative contrast roentgenograms by increased density of the right auricle, not otherwise recognized.

Abstract 11

LEUCINE-INDUCED HYPOGLYCEMIA; SPECULATION ON PATHOGENESIS. Angelo M. Di George, M.D., Victor H. Auerbach, PH.D., and C. Charlton Mabry, M.D., Department of Pediatrics and Physiological Chemistry, Temple University School of Medicine and St. Christopher's Hospital for Children.

During the past two years we have been engaged in the investigation of the phenomenon of leucine-induced hypoglycemia. Cochrane et al. (1) in 1956 first reported that certain children with "idiopathic" hypoglycemia respond to the administration of L-leucine with a distinct lowering of blood sugar level. It is now established that some patients with functioning islet cell tumors are also "leucine-sensitive" (2–4). It has been further established that leucine lowers the blood glucose level by evoking an increase in circulating insulin levels (5).

The present report deals with further studies designed to clarify the mechanism of leucine-induced hypoglycemia. A group of 18 convalescent children (ages 1 month to 7½ years) were administered L-leucine and glycine orally on alternate days. The dose of leucine was 300 mg/kg and the dose of glycine was equimolar to this (172 mg/kg). Capillary blood was collected at 15 minutes intervals over a 1½ hour period and glucose content was determined by the glucose oxidase method. The results are shown in Table I.

A second group of 12 adults (19 to 30 years of age) were tested in a similar fashion. The amino acid was administered as a slurry and venous blood was utilized for the blood glucose determinations. These results are given in Table II.

No significant change in blood glucose levels followed administration of glycine to either group. In contrast, a small but highly significant depression of blood glucose level followed the administration of leucine to both groups. The changes were greater in the

TABLE I

RESPONSE OF NORMAL CHILDREN TO ORAL GLYCINE AND L-LEUCINE

	Time (in minutes)						
	0	15	30	45	60	75	90
Glycine							
Blood glucose (mean in mg %)	73.8	72.9	76.2	76.2	75.1	74.8	75.1
± S.E.M.	2.1	2.2	3.0	2.4	2.2	2.1	2.3
L-leucine							
Blood glucose	74.5	69.7	68.0	66.7	65.3	63.5	66.9
± S.E.M.	2.0	2.6	2.7	2.3	2.5	2.1	2.0
P Value				<0.001	<0.001–0.005	<0.001	<0.001

TABLE II

RESPONSE OF HEALTHY ADULTS TO ORAL GLYCINE AND L-LEUCINE

	Time (in minutes)						
	0	15	30	45	60	75	90
Glycine							
Blood Glucose (mg %)	78.1	78.8	79.0	78.9	78.4	77.6	76.5
± S.E.M.	1.3	0.4	0.9	1.1	2.2	2.4	2.1
L-leucine							
Blood glucose (mg %)	78.6	77.8	76.4	75.3	74.3	73.0	73.5
± S.E.M.	1.2	0.9	1.6	1.5	1.8	2.7	2.2
P Values				0.01–0.02	0.025–0.05	0.01–0.02	0.05–0.10

children than in the adults. It appears that leucine may act as stimulus for insulin release in normal subjects and be a factor in normal homeostasis of insulin production or release, or both. It is suggested that patients with "idiopathic" hypoglycemia or with islet cell adenomas who are leucine-sensitive probably have a derangement of this hemostatic control mechanism.

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Abstract 12

STUDIES OF THYROXINE ANALOGUES, WITH COMMENTS CONCERNING THEIR USE IN PATIENTS WITH CARDIOVASCULAR DISEASES. Marvin L. Sachs, M.D., Department of Medicine, University of Pennsylvania School of Medicine.

Recent interest in the concept of "dissociation" of effects of thyroid hormones has led to clinical evaluation of several derivatives and isomers of thyroxine and triiodothyronine. Alteration of the chemical structure of these "natural" hormones, for example by rearranging the iodine atoms on the rings, by changing the side chain, or by separating D isomers, has resulted in a group of compounds referred to as thyroxine analogues. Impressive evidence from animal bioassays supports the notion that structural changes can differentially influence potency with respect to the separately measured effects.

In the clinical situations in which thyroid hormones might be used in the treatment of patients with cardiovascular diseases, the presence of angina pectoris, cardiac failure or an arrhythmia is often considered to contraindicate these drugs. The usual reason given is that thyroid hormones increase the metabolic rate and stimulate the heart unfavorably. With a variety of analogues of thyroxine available, one must ask if a compound can be found that will allow a greater safety margin than do the natural hormones.

Four possible indications for the use of thyroid hormones will be mentioned: (1) myxedema heart disease, (2) iatrogenic hypothyroidism following thyroidectomy or radio-

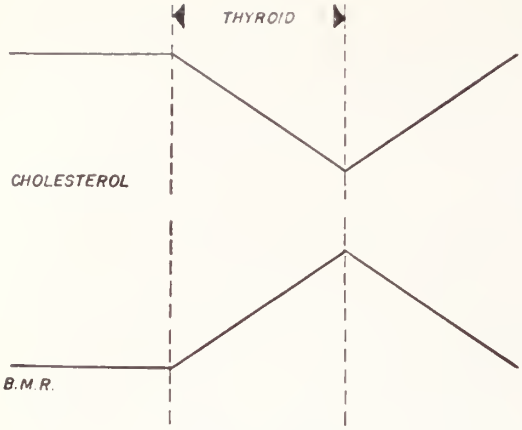

FIG. 1. See text

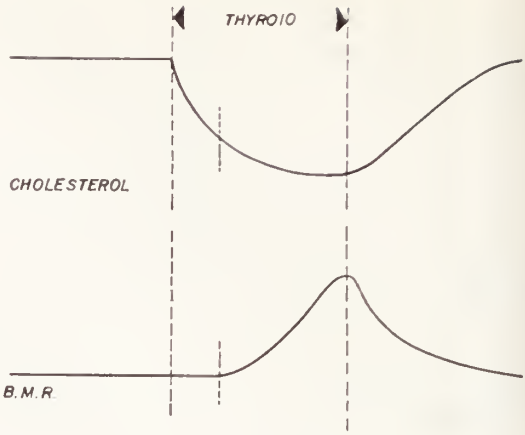

FIG. 2. See text

active iodine treatment of severe angina pectoris or cardiac failure, (3) hypercholesterolemia, (4) atherosclerosis.

1. Myxedema heart disease. This uncommon condition has not been considered a therapeutic problem (except perhaps in the presence of severe arteriosclerotic heart disease) and will not be discussed here as a separate entity.

2. Hypothyroidism following thyroid ablation for angina pectoris or heart failure. The unpleasant symptoms of severe hypothyroidism often cannot be relieved by presently available thyroid preparations without precipitating or increasing the cardiac symptoms. It is not certain that any of the analogues is better than the natural hormones, but we have felt that 3,5,3′-triiodothyropropionic acid satisfactorily relieves the symptoms of hypothyroidism, is especially well tolerated and has the advantage of a short duration of action, so that any untoward cardiac stimulation will be quickly relieved after it is stopped. Perhaps other analogues eventually will be shown to be preferable.

3. Hypercholesterolemia. Without doubt this is the most popular indication at the present time for several thyroxine analogues, and treatment of hypercholesterolemia in patients with coronary artery disease has received major emphasis. It can be said at the outset that all of the thyroactive analogues appear to be capable of producing angina pectoris in susceptible patients, but some may have a relatively greater effect than the natural hormones on lowering serum cholesterol at comparable calorigenic doses.

A hypothetical scheme for the relationship between serum cholesterol and basal metabolic rate under the influence of a thyroactive compound is shown in Figure 1. This hypothesis would hold that there is a simultaneous increase in BMR as serum cholesterol falls, both returning toward the baseline levels when the thyroactive substance is stopped. Our observations on hypothyroid patients treated with 3,5,3′-triiodothyropropionic acid or with 3,5,3′-triiodo-D-thyronine have shown that this scheme is not in fact valid. A more refined concept, at least for the hypothyroid patient, is diagrammed in Figure 2. Almost immediately after the administration of the thyroactive substance, the serum cholesterol begins to fall. The BMR usually does not begin to rise until the cholesterol has already fallen appreciably. Expressed differently, one can say that certain doses of these two analogues (and of other analogues and probably of the natural hormones as well) can be found which are adequate to depress serum cholesterol but not to raise the BMR, at least for limited periods of time.

The analogues mentioned above do depress serum cholesterol levels in euthyroid patients with notable consistency, but the BMR

response is more variable than among the hypothyroid patients. Some cases of familial hypercholesterolemic xanthomatosis respond with a fall in serum cholesterol, but not to normal levels.

4. Atherosclerosis. This condition is being clearly distinguished from hypercholesterolemia, not to imply that the two are unrelated but to point out that no data at all are now available pertinent to the effect of thyroxine analogues on the development of atherosclerosis in humans.

Summary: (1) There is definite use for thyroactive drugs in hypothyroid patients with heart disease, including many with coronary heart disease. There is tentative encouraging evidence that some analogues may be easier and safer to use than L-thyroxine and 3,5,3′-triiodo-L-thyronine (considered the "natural" hormones). (2) The use of thyroxine analogues to treat hypercholesterolemia in euthyroid patients, with or without heart disease, is on uncertain ground at this time. (3) The effect of any thyroxine analogue on the development of atheromatous lesions in humans is unknown.

Memoir of Carl Sheldon Williams (1872–1960)*

By ALFRED COWAN, M.D.

CARL SHELDON WILLIAMS was born in Chatham, Ohio, on May 16, 1872, and died November 8, 1960, in Pennsburg, Pennsylvania, at the age of 88. He was graduated from the University of Pennsylvania in 1895 and received his medical degree in 1897. He studied ophthalmology at the University of Heidelberg, Germany, in 1898; at the Royal Ophthalmic College, London, in 1899; and, later, under Dr. George E. de Schweinitz in Philadelphia. He married Annette Mae Pratt, of California, who died in 1953. Later he married Irma Hemminger, who survives him.

Dr. Williams was very active in his hospital work. He was on the staff of the Germantown Hospital where he was chief of ophthalmology and served for over forty years. He was also on the staff of the Chestnut Hill Hospital and of the Hospital of the University of Pennsylvania. He was elected a Fellow of the College of Physicians in 1907 and, among numerous other societies, was a Fellow of the American Ophthalmological Society since 1910. He served as a Captain in the Air Medical Corps in World War I; later he was a Major in the Army Medical Reserve Corps, until May 8, 1934.

Although Dr. Williams was thoroughly and efficiently trained and was a conscientious ophthalmologist, he was not a writer and so contributed little to the literature, and took no part in the proceedings of any of the medical societies of which he was a member. In his later years he was seldom seen at meetings. He was always pleasant, friendly and modest in his manner, and was liked by all who knew him, but his circle of intimates was small.

Dr. Williams was practically unknown to the present generation of ophthalmologists; in fact he was not well known professionally, even to the previous generation. But in the annals of sports, Carl Williams' name is outstanding. He played football for three years at the University of Pennsylvania and was Captain and Quarterback of the 1894 team. He was one of Penn's all-time great players and coaches. He coached the University's football team from 1902 until 1908, which included the undefeated team of 1904–05. He acted as advisory coach until 1910.

To trace Dr. Williams' many extraprofessional activities would be a long task. He was a keen sportsman. He raised English setter dogs and was President of the English Setter Club of America. Once a year over a long period of time he spent six weeks hunting and fishing in Canada with Dr. Thomas B. Holloway who, as far as I know, was his only crony.

Besides his wife, Dr. Williams is survived by two daughters, Mrs. Ann Morris and Mrs. Jane Rathbun; also one grandson, Christopher Sedgwick Morris, the son of Mrs. Ann and Joseph C. Morris, Jr.

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Memoir of Karl Ernst Paschkis (1896–1961)*

By ABRAHAM CANTAROW, M.D.

KARL ERNST PASCHKIS was born in Vienna, Austria, February 8, 1896, the son of Max and Louise Paschkis. He received his academic and professional education at the University of Vienna, serving also as Demonstrator of Anatomy from 1916 to 1919, in which year he received the degree of Doctor of Medicine. In the subsequent Viennese phase of his professional career he occupied the following positions: Assistant, Department of Anatomy, University of Vienna Medical School, 1920; Intern, Kaiser Franz Joseph Hospital, 1920–1924; Acting Director, Department of Pathology, Kaiser Franz Joseph Hospital, 1924–1925; Resident Physician, Department of Medicine, University of Vienna Hospital, 1925–1931; Assistant in Medicine, Allgemeine Poliklinik, 1931–1938.

Educated in the finest tradition of European academic medicine, and in one of its finest institutions, Doctor Paschkis acquired early an active experience in anatomy, pathology, physiology, and pharmacology, as well as in clinical medicine. As a result of this exposure to a variety of basic science disciplines, he developed a working familiarity with principles and technics of experimentation that in later years was at once the admiration and the envy of his colleagues.

These were bad times for Austria, and the handwriting was on the wall, for all to see. It could not have been easy, at forty-two years of age, with an established professional reputation, an active practice, and a wide circle of friends, to uproot oneself and move thousands of miles to entirely new and foreign surroundings. Many did so, but few managed this transplantation as successfully as Karl Paschkis. He came to Philadelphia in 1938 as a Research Associate at the Fels Institute, Temple University, where he engaged in research in endocrine physiology. In 1940 he went to the Jefferson Medical College, as the J. Ewing Mears Teaching and Research Fellow in Medicine and Physiology. Here he stimulated the development of a program of clinical and research activities in endocrinology, the participants in which were held together mainly by the cementing influence of his broad vision, wide range of interests and experience, infectious enthusiasm, boundless energy, and engaging personality. In a short time, largely through his efforts, the Endocrine Clinic at Jefferson became widely recognized as an important center of research, clinical activity, and training in endocrinology. Appointed Chief of this Clinic in 1942, and actively engaged in the teaching programs of the Departments of Medicine and Physiology, he was advanced progressively in both departments to the positions of Professor of Physiology and Clinical Professor of Medicine, which titles he held at the time of his death.

In 1943, his research interests began to be directed toward certain endocrinological aspects of experimental carcinogenesis and, within a few years, contributions of his laboratories to this field gained such widespread recognition that a division of Endocrine and Cancer Research was established in 1949, with Karl Paschkis as Director. His scientific achievements are recorded in over 200 contributions in professional journals, mainly in the fields of clinical and experimental endocrinology and cancer research. He was also the senior author of a popular text-book of Clinical Endocrinology and a contributor to several other volumes on this subject. He was a familiar figure at virtually all meetings of national and local societies in these fields, and

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participated actively in their discussions and deliberations.

He was a member of the American Physiological Society, American Medical Association, American Association for Cancer Research, Endocrine Society, American Association for the Advancement of Science, Society for Experimental Biology and Medicine, and the New York Academy of Sciences.

Karl Paschkis was a person of scrupulous honesty, with the highest standards of moral and scientific integrity; unwilling to compromise with truth, he was nevertheless always receptive to new ideas, regardless of their source. This is what particularly endeared him to young men, who found in him a willing and indeed enthusiastic audience for the most improbable flights of their imaginations. He had a deep interest in everyone with an intelligently inquiring mind, and a sincere respect for students at every level of educational experience.

He was a fine example of a truly civilized person, gentle, kindly, tolerant, broadly educated, charming, intellectually stimulating, and with a delightful sense of humor. He had an intense interest in and understanding of ancient cultures, developed in his student days and early professional life by travels in Asia Minor, Persia, Afghanistan, and Greece, and in later years by frequent visits to Mexico, Central America, and South America. He loved life and humanity, and their expressions in art, literature, and music. His enjoyment of all of these activities and interests has been shared by his wife, whom he met as a fellow medical student, Margaret Kanitz-Wiesenburg, and married in 1920.

Few men have enjoyed to the same degree the sincere respect and real affection of their peers. He was a scientist of the first rank, a true friend, a delightful companion, and a stimulating teacher and colleague. The manner of his dying was an inspiration to all, as was the manner of his living. From its onset, he had no illusions concerning the inevitable course of the malignant disease with which he was afflicted. Nevertheless, realizing fully that each day might be his last, he continued to extract the maximum of pleasure from each moment and to plan for the future. The world is the better for his sojourn in it, and is the worse for his having left it on January 27, 1961.

Memoir of Chevalier Lawrence Jackson (1900–1961)*

By CHARLES M. NORRIS, M.D.

CHEVALIER L. JACKSON, A.B., M.D., M.SC.(MED.), a Fellow and past Chairman of the Section on Otolaryngology of the College of Physicians of Philadelphia, died suddenly at his home near Schwenksville, Pennsylvania, on Friday evening, January 13th, 1961.

His career was a distinguished and remarkably diversified one. As the successor of his illustrious father, Dr. Chevalier Jackson, he yet achieved his own individual role in the development of the sciences of Laryngology and Broncho-Esophagology. The motivating force of his entire professional life, as in that of his father, was an unselfish ambition to teach and train others.

Born on August 19th, 1900, at Pittsburgh, he enrolled in the University of Pennsylvania shortly after moving with his family to Philadelphia in 1916, graduated from the College in 1922, School of Medicine in 1926, and Graduate School of Medicine in 1930. He was elected to Phi Beta Kappa and Alpha Omega Alpha honor societies during student years. When his father, having established departments at Jefferson Medical College and the Medical School and Graduate School of the University of Pennsylvania, was invited in 1929 to accept a newly created Chair of Laryngology and Broncho-Esophagology at Temple University, Chevalier L. collaborated in the founding of the "Chevalier Jackson Clinic," remaining after his father's retirement in 1937 as Professor and Chairman of the Department of Laryngology and Broncho-Esophagology.

In post-graduate courses at Philadelphia as well as in Europe and Latin America, he promoted methods of safe and efficient bronchoscopy and esophagoscopy, and demonstrated the wide field of application of peroral endoscopy in modern medicine. With John Franklin Huber, he developed and popularized a practical system of segmental bronchial nomenclature which has been universally accepted. He was an author or co-author of seven textbooks which have become standard reference works in the specialty, some of which have been translated into foreign languages, as well as numerous contributions to systems of medicine and surgery.

A dynamic and dedicated teacher and a gifted lecturer, he was also a sympathetic advisor, respected by his associates and colleagues and revered by his patients. Firm in his opinions, he was nevertheless tolerant of the views of others and always receptive to suggestion. As a master of the art of endoscopy, and particularly in problems of foreign body, he met the challenge of the difficult case with consummate skill, as well as by the development and perfection of numerous instruments and techniques. With a background of sound and comprehensive experience in laryngeal surgery, he was responsible for the development of several new operative techniques. In his treatment of patients, he was invariably sympathetic and considerate, feeling a genuine interest in the welfare of the unfortunate.

An enthusiastic and fervent believer in internationalism, both medical and nonmedical, and an accomplished linguist, he devoted great effort to promotion of international societies. Two of these, the Pan American Association of Oto-Rhino-Laryngology and Broncho-Esophagology and the

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International Bronchoesophagological Society, he was instrumental in founding, serving as Executive Secretary of both until the time of his death. A special interest in Latin America won the friendship and admiration of numerous colleagues in Central and South America.

An active member in all of the Societies associated with his specialty, he had served as President of the American Broncho-Esophagological Association and the American College of Chest Physicians, and as Vice-President of the American Laryngological Association, and the American Academy of Ophthalmology and Otolaryngology. Among his prized achievements were membership in twenty-two foreign medical societies and honorary faculty appointments in Chile, Uruguay and Mexico. In 1948 he was made a Commander of the Order of the Liberator San Martín (Argentina), and in 1956 a Chevalier of the Legion of Honor of the French Republic. He was also a member of the Advisory Board of the American Hospital of Paris.

With a breadth of cultural interests rare among physicians, he engaged in numerous non-medical pursuits. He was an active member of the World Affairs Council, the Alliance Francaise and the International House, as well as a founder member of the World Medical Association. He was also a music lover, having been President of the Philadelphia Grand Opera Company from its founding in 1950 until the time of his death.

Mr. Maxwell Ellis, the British laryngologist and a long time friend writes, "He loved people when meeting them for the first time, and even more, meeting them again. He never forgot a name or a face, as hundreds of people all over the world will recall. This was not a studied politician's technique, but the result of a genuine interest in human beings. He was generous to a degree of both his time and resources and rarely refused a call to go and lecture or demonstrate.

"There was thus scarcely a place in the world to which C. L. had not been, complete with his cameras and laden briefcase full of papers and lantern slides, always enthusiastic. In giving himself so lavishly to life, the inevitable happened. A coronary attack which might have made some men invalids for life merely exasperated him, and certainly exerted no check on his subsequent activities.

"It seemed so painfully clear that suddenly, hurrying on some air field or dashing for some taxi probably many thousands of miles from home, the end would come, but at last, it was in his home, after a day spent working at his desk, that in the evening he sat forward in his arm chair, gasped and died. And Laryngology has lost one of its most remarkable and lovable characters, and many of us have lost a great friend".

Memoir of Carroll Richard Mullen (1900–1961)*

By THEODORE R. FETTER, M.D.

CARROLL R. MULLEN was born in Bloomington, Illinois, November 9, 1900, the son of Thomas Robert Mullen, M.D., and Margaret Carroll Mullen. During his adolescence he was a resident of Omaha, Nebraska, obtaining his preliminary education at Creighton Preparatory School, Omaha, Nebraska. He received a Bachelor of Arts degree from Creighton University in Omaha, and his degree of Doctor of Medicine at Jefferson Medical College of Philadelphia in 1926. He served as Intern and Resident Physician at the Philadelphia General Hospital during 1926 to 1928. Following completion of his internship and residency, Doctor Mullen opened and maintained offices in Philadelphia until his death, February 1, 1961.

As a member of the Executive Faculty of Jefferson Medical College of Philadelphia at the time of his death, Doctor Mullen held the post of Professor and Head of the Department of Ophthalmology at the College and Attending Ophthalmologist-in-Chief to Jefferson Medical College Hospital. He also served on the staffs of other local hospitals: Executive and Attending Surgeon to Wills Eye Hospital, Active Consultant in Ophthalmology to Philadelphia General Hospital, and Consultant in Ophthalmology to Veterans' Administration Hospital of Philadelphia and the J. Lewis Crozier Hospital, Chester, Pennsylvania. He was a Charter Staff Member of Fitzgerald-Mercy Hospital in Darby, Pennsylvania.

Dr. Mullen was an interested and active member of the Alumni Association of Jefferson Medical College. In 1953–1954 he served as National President of the Association. He was also a member of the Executive Committee of the Association, and in 1959 was named Chairman of the Annual Giving Fund Committee.

Doctor Mullen was a Fellow of the American College of Surgeons, the American Academy of Ophthalmology and Otolaryngology, and the College of Physicians of Philadelphia. He was a Diplomate of the American Board of Ophthalmology; a member of the Association for Research in Ophthalmology, the Pennsylvania Academy of Ophthalmology and Otolaryngology, the American Medical Association, the Philadelphia County Medical Society and the Medical Society of the State of Pennsylvania. He served as Chairman of the Section on Ophthalmology of the College of Physicians of Philadelphia from 1959 to his death.

Doctor Mullen's extramural activities were varied. He was a member of the Union League of Philadelphia, the Friendly Sons of St. Patrick, the Catholic Philopatrian Literary Institute, and the Skytop Club.

Although Doctor Mullen's professional life was active and demanding, he found time to participate in civic affairs. He was a Life Trustee and Director of the Free Library of Philadelphia, a member of the Advisory Board of Lay Trustees of Villanova University, and a Governor of Creighton University Alumni Association. In 1959 he was elected a member of the Board of Directors of City Trusts.

Doctor Mullen was also a Director of the Aid Association of the Philadelphia County Medical Society and a member of the Alpha Kappa Kappa Medical Fraternity.

Doctor Mullen was an outstanding character among Philadelphia physicians. His particular gifts in executive and professional promotional activities were noteworthy. These attributes were evident in the transactions of the Aid

* Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

Association of the Philadelphia County Medical Society, the Free Library of Philadelphia, the Board of City Trusts, with special emphasis on the needs of Wills Eye Hospital, and his tremendous interest in his *Alma Mater*—Jefferson Medical College of Philadelphia. He gave unstintingly of his time and talents to civic, religious and professional activities. Indeed, it may be said without exaggeration that he exemplified the type of physician which any community could very well be proud to claim as one of their outstanding public spirited citizens. His personal friendships were highly valued.

He is survived by his wife, the former Helen M. Dougherty; two daughters, Mother Susan Carroll Mullen, Religious Order of the Sacred Heart of Jesus, Albany, New York, and Mrs. William Michael Carney, Jr., of Rosemont, Pennsylvania; two granddaughters, Margaret Carroll Carney and Susan Eleanor Carney; a brother Dr. George C. Mullen of Evanston, Illinois, and a cousin, Dr. George P. Carroll of Omaha, Nebraska.

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Contributions of Biochemistry to Psychiatry[1]

By SEYMOUR S. KETY, M.D.[2]

THE REVOLUTION which modern biochemistry has incited in clinical medicine can be compared in significance and achievements to such other great advances as the dissection of the human body, the discovery of the microscope, or the concept of the microbial origin of infectious disease. Knowledge of the internal chemical environment of the body, prompted and elaborated by the queries and investigations of pediatrics only three decades ago, has repaid that investment many times over in the practical achievements it has introduced to that specialty, to surgery and to most of the others. The diagnostic value of chemical studies, the understanding of metabolic mechanisms in pathogenesis and the bases which they have raised for rational therapy have made themselves indispensable to the practice and development of medicine generally.

It would be conveying false information to suggest that the influence of biochemistry in psychiatry was as great as that which it has properly maintained in the other branches of medicine. Yet within our lifetime two mental disorders have yielded to the biochemist in terms of etiology, diagnosis, and prophylaxis. Pellagra, the mental aberrations of which once accounted for 10% of the institutionalized mentally ill in large areas of this country, has all but disappeared and the residue which remains lies at the doorstep of the educator and the legislator rather than the biochemist. In the conglomerate field of mental retardation one small segment has been found to be associated with an inability to convert phenylalanine to tyrosine, simple chemical tests have been devised for its diagnosis and the identification of the heterozygous carriers and considerable progress has been made in its prevention by dietary methods. But psychiatry deals with many more problems than pellagra or phenylketonuria and the contribution of biochemistry to these problems where it is appropriate remains to be made.

Thudichum, the founder of modern neurochemistry, firmly believed that many of the mental disorders were the result of metabolic errors and their resultant chemical toxins. But he also wrote that these defects would be demonstrated "after we know the normal chemistry to its uttermost detail." (1) The contributions of chemistry to psychiatry will best be designated after the problems of psychiatry have been solved. Only then will it be possible to trace all of the paths from basic discoveries to practical accomplishment. Before

[1] Alvarenga Prize Lecture XXI, College of Physicians of Philadelphia, 4 October 1961.

[2] Professor and Chairman, Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore 6, Maryland.

that time, however, it is nonetheless possible to state with a fair degree of certainty that to do what Thudichum required to be done, to try to understand the normal chemistry of the brain to its uttermost detail, cannot help but contribute to an understanding of normal and abnormal behavior. I should like at this time to review in a rather sketchy manner some of the developments which have occurred in the understanding of the biochemical processes which underlie behavior. This study began as it properly should have begun with attempts to learn about the composition of the brain and of nervous tissue. It was Thudichum again who began an exhaustive program which was to take him more than 20 years of extraction, isolation and analysis of the brain. For this he was much scoffed at by some of the leading biochemists of his day who said that to attempt a chemical analysis of the brain was about as useful as analyzing bread and butter. Many of the compounds which have played a prominent role not only in the nervous system but in the biochemistry of other organs and systems were substances which were first discovered by Thudichum in the brain—sphingosine, cephalin, to mention just two. The predominance of lipids in the structure of the brain was very early noted in these studies and today we are beginning to realize and to a considerably less extent to elucidate the role which lipoprotein interfaces may play in the development and maintenance of the ionic disequilibria which form the basis of the electrical coding system by which the brain carries out its unique function of communication of information among its parts and with the outside world.

Interest in the energy metabolism and respiration of the brain developed rather early, going back even to the active debates between the mechanistic and vitalistic schools in which the fundamental nature of mental processes was an active arena.

Mosso (2) by placing delicate mercurial thermometers into the brains of living animals gathered evidence from which he postulated that the brain was the seat of active metabolic processes. With the development of techniques for the study of tissue respiration, Mosso's prediction was confirmed in the brain slice (3), in the isolated sympathetic ganglion still capable of performing its normal function (4), in the isolated perfused brain of animals (5) and in man under physiological conditions (6). Not only was it found that the nervous system used energy at a rate higher than that of most other organs in the body, but also that there were special features about its metabolism which if not unique were shared by only one or two others. I refer to the observation first suggested by the respiratory quotient of unity found quite consistently in the studies *in vitro* and later confirmed by measurements in animals and man, that glucose provided the only significant substrate for the energy supply of the brain and that normal cerebral function was extremely sensitive to the constant supply of this foodstuff to the brain (7). This did not preclude the existence of other pathways of metabolism for the replenishment of structure and for the many specialized functions within the brain, and an active turnover of amino acids and of protein as well as lipids has been demonstrated (8) although of course the magnitude of all of these is small in comparison with the oxidation of glucose.

In recent years there has come a realization of the importance of the dimension in which the brain is truly unique—its magnificent organization. The great advances which biochemistry has experienced were made to a very large extent upon two organs, the muscle and liver, in which interestingly enough the biochemical processes taking place within the cell are a good representation of the biochemistry of the whole. The liver slice and the muscle spindle go on being liver and muscle in the Warburg flask or perfusion chamber, at the same time permitting an examination of the biochemical processes which underlie their functions. But the brain more than any other organ is far greater than the sum of its parts, since most of its special functions lie not in its component cells but in the connections and interrelationships among them. Knowledge of the metabolism of the brain slice or even of the

brain as a whole is only the beginning of an understanding of the relationship of biochemistry to function in that organ just as the early studies of the BMR laid a foundation to, but hardly hinted at the richness of the biochemical superstructure which was to come. Recently in our own laboratory at the National Institute of Mental Health some of us had begun to outline the highly differentiated metabolism occurring within the brain during life (9). In Figure 1 there is an example of a map of the regional circulation of the brain, but since there is reason to believe that under normal conditions the circulation accurately follows the metabolic needs the same figure represents the varied rates of metabolism which occur there. But with much greater delicacy the highly specialized aspects of metabolism are beginning to be mapped "to their uttermost detail," by the magnificent techniques of Lowry (10) who borrowed the microchemical approach which A. N. Richards had used so successfully in elucidating the function of an individual nephron and refined it and extended it to an examination of the biochemical patterns of the single neuron. In order to do this he had to develop methods for dissecting out

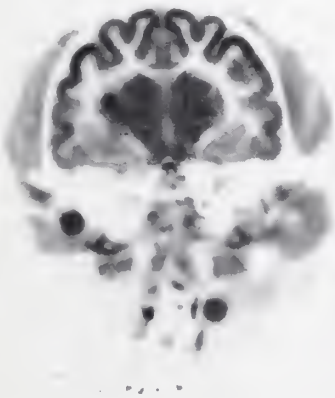

Fig. 1. Autoradiogram showing the distribution of CF_3I^{131} in a section of the brain of a cat exposed to the gas for 1 minute before sacrifice. Regional circulation is the major determinant in that distribution under the conditions employed.

and weighing these individual cells and then for analyzing them for a large variety of enzymes and substrates. Others, meanwhile, were studying the distribution of special substances, pharmacologically active elsewhere in the body, and speculating upon their role in neural function. Acetyl choline with the two enzymes necessary for its synthesis and destruction was probably the first of these substances to be examined (11). But in the last decade and in staccato fashion we have learned about the presence and provocative distribution of gamma amino butyric acid (12), serotonin (13), noradrenalin (14), and the enzymes which mediate their concentration in highly specialized regions throughout the brain.

I like to think sometimes of a clinical problem like schizophrenia or the depressive psychoses as one or more islands of knowledge in the unknown. A mainland surrounds these islands but at some distance and this mainland represents the body of fundamental knowledge. This mainland, which represents many disciplines, will someday provide the base from which a number of bridges will span the gap to the clinical problem. And the kind of information of which I have been speaking represents that region of the mainland which we call biochemistry. In addition, there have been many caissons launched into the unknown seeking to build the foundation for some of these future bridges. How many of these will succeed in their mission and how many will find that they have settled upon a soft and insubstantial bed we do not know, but we do know that without them the bridge will not come about. I should like to describe some tentative pilings which are being thrust into the unknown which lies between basic biochemistry and the problems of human behavior.

Let me begin with the fascintaing problem of memory. It has been known for some time that a learned pattern of behavior in animals or a group of nonsense syllables in man, if not otherwise reinforced appears to decay in a roughly exponential manner. Since unstable or quasi-stable chemical compounds decay along

the same type of curve in the familiar monomolecular reaction, many have suggested for some time that perhaps memories are stored as chemical traces of some kind within the brain. Attempts were made in cold-blooded animals to learn whether the decay of learned performance was speeded by rise and retarded by a fall in temperature as would be a chemical reaction, but these results were inconclusive. The concept was to a very large extent abandoned until very recent times when knowledge of the protein molecule and its synthesis reawakened it. There are many reasons which would make the protein molecule and ribose nucleic acid which is its template likely candidates for the chemical mechanism in information storage. These are the only types of molecule which we know which have the size and complexity to permit an almost infinite degree of individuality and the meaningful sequence of amino acids or nucleotides they contain offered the possibility of a remarkable and efficient coding system which would be necessary for information storage. Furthermore, examples were known in biology where the protein molecule was or appeared to be a transmitter of encoded information. The development of specific protein antibodies and the ability of the organism to regenerate them in response to need at a later time is an example of a form of biological memory which the very term anamnestic response recognizes. A more cogent example, perhaps is the transmission of the tremendous profusion of genetic information from parent to offspring and the evidence which is almost daily being strengthened that this genetic information is encoded in highly specialized DNA molecules of the chromosomes and retrieved in the synthesis of protein from them. The evidence for the intervention of RNA and specific protein synthesis in information storage and retrieval in the brain is much more fragmentary. Very recently F. O. Schmitt at the Massachusetts Institute of Technology has isolated from the neurone a complex protein which has many of the physico-chemical properties required for a memory protein (15). Furthermore, it seems to constitute the delicate neurofibrils within the neurone which interestingly enough appear characteristically to be disrupted and fragmented in certain disorders like Alzheimer's disease in which disturbance of the memory process appears to be a cardinal feature. Dingman and Sporn (16), when they were medical students in the Department of Psychiatry at the University of Rochester, carried out an ingenious series of experiments which support the association between protein synthesis and memory. They showed that the anti metabolite 8-Azaguanine was rapidly incorporated into the RNA in rat brain following its parenteral administration. They then demonstrated that during the period of maximal incorporation of this substance into RNA which would presumably interfere with the ability of the brain to synthesize appropriate RNA configurations, the animal showed significantly decreased ability to learn a new task even though the performance of a previously learned task was unaffected. The inhibition of new learning by 8-Azaguanine was transient and coincided with the period of its maximal activity in the brain. More recently Corning and John, interestingly enough at the same University, demonstrated a deterrent effect of ribonuclease on the learning process (17). Planaria, the little ciliated flat worms that psychologists have taken to studying lately, can be taught a simple conditioned response and are also capable of learning a T-maze. What is more remarkable is that when one of these trained and "sophisticated" organisms is transected, each half will develop into a whole organism which retains the learning. That this learning has somehow been incorporated into the regenerated portion is demonstrated by the fact that if the new organism is once more transected the new half as well as the original half retains the experience and can transmit it to the regenerated organism of which each will be a part. What Corning and John found was that if regeneration was allowed to progress in a dilute solution of ribonuclease, an enzyme which inhibits the synthesis of RNA, a concentration of the enzyme could be found at which regeneration

took place but there was no transmission of the stored learning. This again supports the idea that learning is somehow associated with the synthesis of RNA. Although none of this evidence proves this relationship, there are enough independently arrived at observations which support it to make it an attractive hypothesis and one which well merits continued attention.

In the last decade the phenomenon of consciousness has found some new correlations in the anatomy and physiology of the brain. As the result of the pioneering work of Moruzzi and Magoun (18), consciousness appears to have left its abode in the cerebral cortex where Sherrington had ensconced it and has taken refuge in the unmapped wilderness of the central reticular formation. In the same period of time there have been some much more modest contributions to the problem from biochemistry which, though they hardly explain the phenomenon, have demonstrated at least a relationship between it and cerebral energetics. Many collaborators and I and a number of independent groups have in the past ten or fifteen years measured the oxygen consumption of the brain in man under a variety of physiological states and in a number of pathological conditions. If we arrange the average values in descending order as shown in Table I there is a rough correlation with the level or intensity of the presumed conscious state. The normal value corresponds to an energy utilization of about 20 watts and an interference with the power supply to the brain is almost invariably associated with an alteration in consciousness. The converse is not true, however, for we have found many conditions where consciousness or mental activity is altered and which cannot be attributed to a change in a function as general and fundamental as the overall energy metabolism. In Table II are presented a number of such states. It was these observations which brought home to me that whereas the function of other organs was to do work or to move things whether it be blood, or bone, or ions, the function of the brain was to receive and encode and to store and to communicate information and that the ability of such an instrument to operate effectively although it was dependent upon energy supply was not necessarily correlated with it.

TABLE I

Cerebral Oxygen Consumption and Mental State

Condition	% of Normal
Senile psychosis	82
Diabetic acidosis	82
Insulin hypoglycemia	79
Artificial hypothermia	67
Surgical anesthesia	64
Insulin coma	58
Diabetic coma	52
Alcoholic coma	49

TABLE II

Cerebral Oxygen Consumption and Mental State

Condition	% of Normal or Control
Normal sleep	97
Schizophrenia	100
LSD psychosis	101
Mental arithmetic	102
Anxiety	118
Epinephrine infusion	122

It is in the field of the emotional states that biochemistry seems likely to make its most significant contributions to psychiatry in the immediate future. The idea of chemoreceptors in the brain, highly circumscribed areas especially adapted to perceive and respond to specific chemical substances in the blood, is not a new one. The respiratory centers of the medulla are examples of some of the earliest of these areas to be discovered and studied. More recently Anderson (19) has elucidated areas in the supraoptic portion of the hypothalamus which are sensitive to osmotic pressure and which when stimulated by the local infiltration of minute quantities of hypertonic salt solution cause the animal to drink copiously of water in what appears to be the artificial production of thirst. In 1905 Freud (20) wrote "we may now believe that in the interstitial tissues

of the gonads special chemical substances are produced, which, when taken up in the blood stream, charge definite parts of the central nervous system with sexual tension." Whether or not their purpose was to prove Freud right, Harris, Michael and Scott (21) have in fact done so in some remarkably ingenious experiments on castrated female cats. Such animals lose their characteristic behavior in response to a male but the behavior patterns which apparently are still present in the nervous system can be elicited by the injection of estrogen. Feeling that this humor must be acting somewhere in the brain to trigger the appropriate behavior, these investigators probed the brains of such animals with needles to the point of which were fixed minute crystals of estrogenic substance. Although most of the brain was indifferent to these crystals, when they were implanted within certain areas of the hypothalamus which remain to be further identified, an integrated sequence of normal mating behavior was evoked by an appropriate external stimulus.

Although their role in emotional state or in behavior is at present only speculative, the biogenic amines in the brain form a topic of considerable current interest. The substances have active pharmacologic effects elsewhere in the body and exist in the brain in appreciable concentration. Moreover, their distribution is by no means uniform but appears to be highly differential suggesting important relationships to specific function. Interest in their possible functional role has been further stimulated by the observation that some drugs which produce important effects upon mental state are also associated with changes in the concentration of certain amines in the brain. Two amines have occupied the center of the stage thus far and these are norepinephrine and serotonin. There is good reason to believe, however, that other amines such as dopamine and normetanephrine which stand immediately before and after norepinephrine in its metabolic geneaology may have important functional roles and the possibility always exists that other amines as yet unidentified may represent the crucial ones in terms of function.

It is possible to attribute much of the present interest in the brain amines to two recent discoveries. The first is the finding by Shore and his associates (22) in Brodie's laboratory that the administration of reserpine to animals is associated with a rapid release of serotonin as well as other amines from the brain. The second was the finding by Zeller and his associates (23) that iproniazid, which was known to be a euphoriant drug, was also a monoamine oxidase inhibitor. It has since been shown repeatedly that iproniazid and other monoamine oxidase inhibitors can raise the levels of serotonin or norepinephrine in the brain of a number of species. It is reasonable that these observations should have suggested that specific brain amines modulate mood and explain the central nervous effect of reserpine, iproniazid and their congeners and a great deal of additional evidence has been amassed in an effort further to define the possible relationships. It would be foolhardy to attempt to review a field as active and controversial as this one in a short time and without doing serious injustice to the information which has been acquired. A clearcut and generally accepted principle of the functional role of any of these amines in mood or behavior is not yet possible (24), but the evidence leaves little doubt that these agents find themselves in the brain not by accident and one can predict with a certain degree of confidence that the active work which is continuing in this area is sound and will be productive.

Long before the presence of amines in the central nervous system was established, however, their presence in the circulating blood was known and in the case of the catecholamines, epinephrine, and norepinephrine, a relationship between their presence in circulating blood and mental state had been suggested. That the circulating catecholamines play some roles in states of anxiety is suggested by certain similarities between these states and the effects of administration of epinephrine parenterally to man. There are comparatively few studies

which have sought correlations between blood levels of these catecholamines and the immediate emotional state, and those which have been reported are by no means simple. Mason and Hamburg and their collaborators (25) have recently obtained excellent evidence for the differential appearance of epinephrine or norepinephrine in the blood of animals and man in response to certain anxiety-provoking situations. The relationships as they have determined them are not simple and indiscriminate ones, the appearance of one or the other or of both catecholamines depending upon subtle variables in the situation or subject, such as novelty, expectancy, opportunity of escape or avoidance. If one were permitted a teleological speculation, it might be that epinephrine is made available in situations where fight or flight may be required or possible (and where its ability to mobilize glucose and increase muscle blood flow would be advantageous) while in circumstances where the outcome is inevitable and where aggressive or aversive behavior would be inappropriate or wasteful, norepinephrine appears in high levels in the blood (in anticipation, perhaps, of hemorrhage).

These studies suggest that the endogenous secretion of these two catecholamines bears an important relationship to mental state, and the abilty to measure such secretion under a variety of clinical conditions would represent a significant contribution to psychiatric research. Epinephrine and norepinephrine are to a small extent excreted unchanged in the urine and their measurement in that fluid has been used as an approach to their endogenous secretion (26). Unfortunately, since more than 95% of these amines are metabolized before excretion, the few per cent which are excreted unchanged are more likely to be affected by factors such as renal clearance and blood flow to liver and muscles than by endogenous production. Measurement in the urine of a substance or substances which account for nearly all of the endogenously produced catecholamines would provide a useful index of their endogenous production.

I should like to turn now to the hypothesis that abnormal metabolites of circulating epinephrine act as etiological factors in schizophrenia. This hypothesis has much to recommend it, incorporating as it does the evidence for genetic as well as sociological factors in the development of this group of mental disorders. It was first postulated by Smythies on the basis of similarity in structure between mescaline and the catecholamines and, after he was joined by Osmond and Hoffer, evidence was adduced that adrenochrome, an oxidation product of epinephrine, was hallucinogenic so that this substance or a derivative of it, adrenolutin, was suggested as the toxic substance in schizophrenia (27). The hypothesis had also been supported by reports of a more rapid degradation of epinephrine added *in vitro* to the serum of schizophrenic patients as opposed to normal serum (28), although that phenomenon was subsequently shown by McDonald (29) and others to be more clearly related to the level of ascorbic acid in the diet and in the plasma than to the presence or absence of schizophrenia. The oxidative conversions of epinephrine to adrenochrome and adrenolutin can be produced by the organic chemist *in vitro* but there is little direct evidence for their production *in vivo* whether by normal individuals or schizophrenic patients. In 1956 when we became interested in the problem, it appeared that a crucial test of the hypothesis would be to study the metabolism of circulating epinephrine in schizophrenic patients. This was difficult to do because at that time little or nothing was known about the normal metabolism of epinephrine and only three per cent or so of injected epinephrine, as I have indicated earlier, could be accounted for in the unchanged amines in the urine, more than 95% being converted to unknown compounds. It was immediately apparent that with a substance as pharmacologically active in minute amounts as is this one, which is present in such infinitesimal amounts in the body, the use of isotopic techniques would be advantageous but that it would require an epinephrine of much greater specific activity than the labeled material

which was then available. After a large number of inquiries I was able to get the New England Nuclear Corporation to develop a novel synthesis of tritiated epinephrine which they felt would have sufficient specific activity for our purposes. My most important contribution to this problem, however, was to reawaken the interest of one of my colleagues, Julius Axelrod, in the metabolism of catechol amines. Then at this very propitious time Armstrong, McMillan and Shaw discovered the first major metabolite of norepinephrine in the urine of a patient with pheochromocytoma (30). This compound, 3 - methoxy - 4 - hydroxymandelic acid, was norepinephrine which had suffered two important changes—a methylation in the 3 position and a deamination. Choosing to ignore the obvious pathway by which this compound could arise, Axelrod postulated a novel step of O-methylation as the first transformation which epinephrine underwent and then proceeded to search for and find the resulting compound, O-methyl epinephrine or metanephrine, as he called it, which turned out to be another major metabolite (31). He also investigated the enzymatic processes involved in this conversion and within two years had worked out the major and minor pathways for the degradation of epinephrine in the body (32). The compounds which he and his collaborators identified in the urine account for 98% of the epinephrine which is injected and presumably for the metabolism of endogenous epinephrine as well. In Figure 2, which is taken from Axelrod, is a diagram of the normal pathways in the metabolism of epinephrine which have been shown to exist in a number of species including normal man (33).

With this information of its normal metabolism plus the techniques which he had developed for the separation of the various metabolites, it was now possible to study the metabolism of circulating epinephrine in a population of schizophrenic patients, comparing them with a similar group of normal volunteers following the infusion of small and physiological amounts of the tritium labeled epinephrine (34). In Figure 3 is presented a

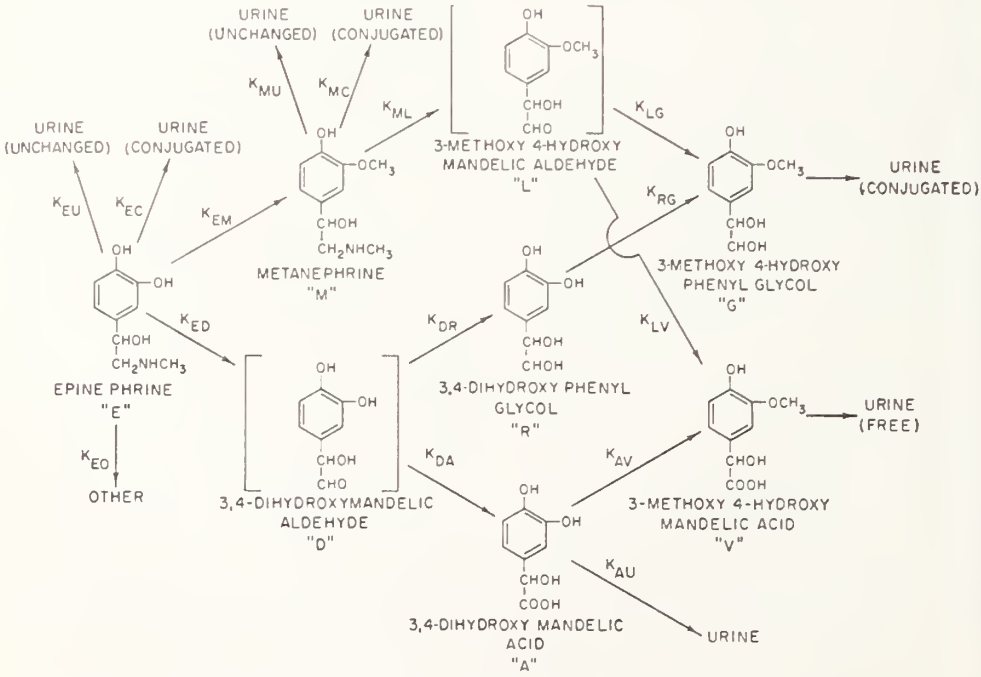

FIG. 2. The metabolic pathways involved in the degradation of circulating epinephrine (After Axelrod)

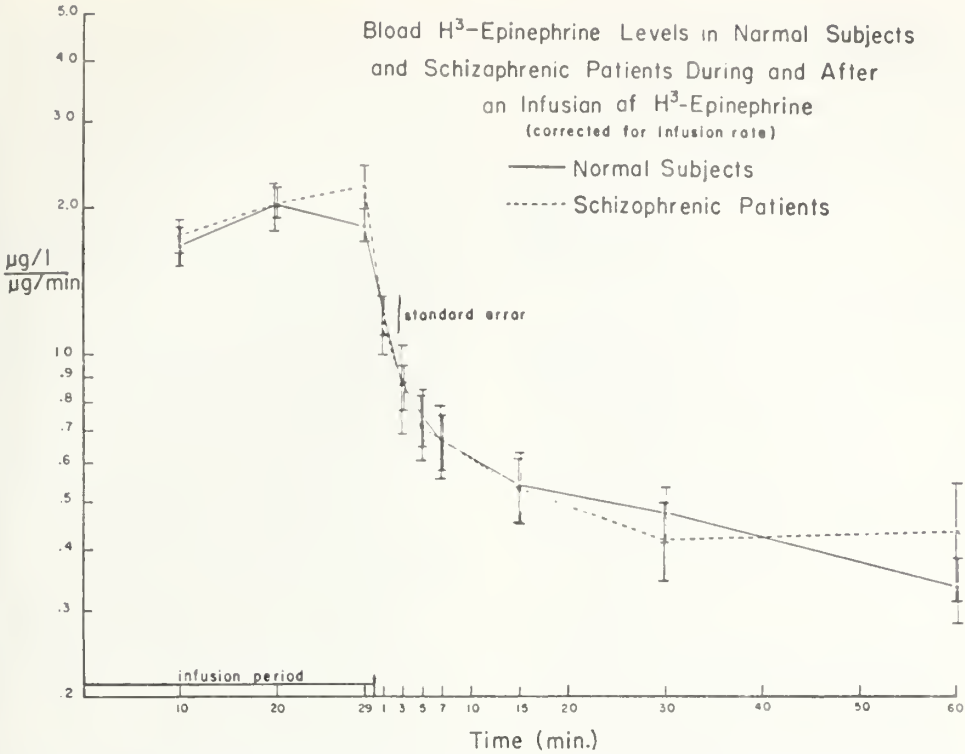

FIG. 3. Blood levels of H^3-epinephrine during and following its infusion in normal and schizophrenic subjects (From LaBrosse, Mann and Kety (34))

summary of the results on the rate of decay of the labeled epinephrine in the circulating blood of both groups following its abrupt withdrawal. There is a rapid decay in both groups and no significant difference between them giving no support to the thesis that the oxidation of epinephrine demonstrated by some groups *in vitro* to be more rapid in the plasma of schizophrenic patients represents a situation which occurred *in vivo*. However, although the rate of decay might be the same the nature of the metabolic products might still be different. In Table III is summarized the metabolites of the infused epinephrine found in the urine in both groups and the means of each. It is apparent that these metabolites which together account for 98% of the activity appearing in the urine are not qualitatively or quantitatively different in the schizophrenic from normal and that there is very little room for a conversion of significant amounts of the epinephrine to adrenochrome, if in fact that process occurs at all.

This study failed to support the interesting epinephrine hypothesis on the etiology and pathogenesis of schizophrenia. The work was hardly in vain, however. As a result of his interest Axelrod was able to elucidate the normal pathways of metabolism for these important agents, and from that to embark upon a program of research in the secretion of catecholamines and their inactivation as effected by physiological and pharmacological influences which has been little short of remarkable in its productivity and importance. Of special interest to psychiatry is the characterization of the 2 or 3 major metabolites of epinephrine or norepinephrine which together account for nearly 90% of the amount of these agents which are released in the body. The estimation of metanephrine, normetanephrine, and 3-methoxy-4-hydroxymandelic acid in the

TABLE III

COMPARISON OF URINARY METABOLITES BETWEEN NORMAL SUBJECTS AND SCHIZOPHRENIC PATIENTS AFTER INFUSION OF H^3-EPINEPHRINE

Mean Per cent of the Total Radioactivity in the Urine

	Normals (12 Subjects)	Schizophrenics (12 Patients)
Metanephrine		
Free	5.2	5.8
Glucuronide	6.0	8.8
Sulfate	29.5	28.7
Total	40.8	43.3
3-methoxy-4-hydroxymandelic acid	41.2	37.5
Free epinephrine	6.8	6.6
3-methoxy-4-hydroxyphenylglycol	7.1	8.9
Dihydroxymandelic acid	1.6	1.7
Total per cent H^3 in urine accounted for by the above metabolites	97	98
Per cent of infused H^3 excreted in the urine	93	87

urine will permit a highly reliable estimate of the endogenous production of epinephrine and norepinephrine in various clinical states and under various physiological and pathological conditions. Methods for the convenient determination of these compounds in the urine have been worked out by a number of different groups and one looks forward to their application to psychiatric, medical and surgical problems with a great deal of interest.

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Heritable Disorders of Connective Tissue[1]

By VICTOR A. McKUSICK, M.D.[2]

IT IS my first and pleasant task to express my gratitude for the invitation to deliver this lecture. I feel it an honor to address this ancient and distinguished society and to speak in memory of Dr. James M. Anders. With his broad view of medicine, Dr. Anders would, I have a feeling, be much interested in the topic of tonight's discussion.

In recent years connective tissue has attained the status of an organ system. Its basic non-cellular constituents are collagen, elastic fiber and the ground substance of whose several components mucopolysaccharide has been most intensively investigated. Of course, the organization of the several non-cellular elements of connective tissue varies from area to area in the organism, witness the differences of bone, tendon, cornea, aortic media and corium, to cite but five. It has come to be appreciated that as an organ-system connective tissue is subject to diseases peculiar to itself—some predominantly acquired and some predominantly heredity in etiology and pathogenesis. The rheumatologist has laid relatively undisputed claim to the connective tissue organ-system and by this right of domain has in recent years acquired some of the social respectability, in the community of subspecialties, long enjoyed by neurologists, cardiologists and others with an "important" organ system to call their own.

In this discourse we are concerned with the hereditary disorders of the connective tissue system and more specifically with those disorders which probably represent generalized disorders of one element of connective tissue: collagen, elastin, or mucopolysaccharide.

Hereditary disorders tend to have a significance to biology and medicine out of all proportion to their numerical significance because they represent potentially pinpointable defects in a biochemical mechanism. Elucidation of the defect often sheds light also on the normal mechanisms and opens up vistas of general biological principles. Alkaptonuria is a rare disorder, but its study led Garrod to one of the major contributions of medicine to biology in this century—his inspired concept of inborn errors of metabolism, essentially the doctrine of "one-gene-one-enzyme" as formulated 40 years later by Beadle.

The five disorders we will be discussing are rare but their study helps clarify our thinking about and extends our knowledge of connective tissue, although it must be granted that no outstanding new principles have been forthcoming.

There is another reason that heritable disorders of connective tissue are of more significance to clinical medicine than might be thought on the basis of prevalence alone: just as connective tissue is ubiquitous in the organism—even the envelopes and blood vessels of the central nervous system contain it—so that manifestations of these five generalized heritable disorders of connective tissue may bring the patient to any one of ten or eleven specialists—neurologist, ophthalmologist, dermatologist, hematologist, cardiologist, gastroenterologist, orthopedist, general surgeon, dentist, otologist, endocrinologist. In few groups of disorders is the broad view of the generalist more essential to proper diagnosis and management.

THE MARFAN SYNDROME

It was in 1896 that a Parisian pediatrician, Marfan, described the skeletal features of the syndrome that bears his name. In the next 50 years the nosography of the Marfan syndrome

[1] James M. Anders Lecture XL, College of Physicians of Philadelphia, 5 April 1961.

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was elaborated to the point that a rather precise clinical delineation is now possible.

The individual who falls heir to the single mutant gene responsible for this disorder may show manifestations of its effects principally in three areas: the skeletal system, especially excessive length of the extremities; the eye, especially dislocation of the lens; and the cardiovascular system especially a weakness of the aortic media which may lead to dissecting or diffuse aneurysm of the aorta or a combination of the two. See Figure 1, 2 and 3.

All three areas may not show clinically evident changes in a given patient. As in most disorders inherited as Mendelian dominant traits the range of variation in severity is wide. Within limits the degree of severity of the ocular, skeletal and aorta manifestations may vary independently of each other.

The ratio of upper segment to lower segment, measured from the pubic symphysis, is a useful index of the skeletal manifestations of the syndrome. However, there is considerable overlap with the normal measurements and the normal values are different for whites and the American Negro.

The first part of the aorta to undergo progressive dilatation in the Marfan syndrome is usually the very base in the region of the sinuses of Valsalva and the aortic valve seat. Since this portion is situated well within the cardiovascular shadow, the patient with the Marfan syndrome may have marked aortic regurgitation with no or little evidence of dilatation of the aorta by ordinary radiographic means.

Aortic aneurysm in this condition is not a congenital malformation in the usual sense. The fundamental weakness of the aorta is undoubtedly present at birth—and therefore "congenital" in the strict sense—although it is not certain that histologic studies in early life reveal any recognizable abnormality. It is the combination of physiologic hemodynamic stress with the genetic weakness which leads to the progressive dilatation of the aorta, interrupted in some cases by catastrophic rupture.

Undoubtedly the connective tissue defect underlying this clinical syndrome of Marfan is generalized and specifically the entire aorta undoubtedly has the same defect of the media. The explanation for the predominant localization of change in the ascending aorta is probably to be found in the concentration there of hemodynamic stress of a particular type. The ascending aorta undergoes more expansile pulsation with each heart beat than any part of the arterial tree beyond the aortic arch where the pulse is, as it were, "bled off" in part. Under this repetitive stressing the genetically defective aorta undergoes what the construction engineer would term "structural fatigue."

The Marfan syndrome is inherited as a simple Mendelian non-sex-linked dominant trait. On the average half the children of an affected person can be expected to inherit the trait. Rather numerous sporadic (or isolated) cases occur. Some of these may be new mutations. Others are probably clever non-genetic facsimiles of the genetic disorder. In the absence of a pathognomonic test to aid in identifying mildly affected persons and to confirm the fact that all cases have fundamentally the same disorder it is difficult to estimate frequency. The Marfan syndrome may have a frequency about the same as hemophilia, that is, about 1 in every 15,000 births, although one survey—done in Northern Ireland—set the frequency appreciably lower.

What is the basic defect? The change observed in the aorta would tend to incriminate the elastic fiber which appears to degenerate. Three laboratory abnormalities—two biochemical, one chromosomal—have been reported. Low serum mucoprotein (better termed *seromucoid*) reported by Bacchus in the affected members of one sibship could not be confirmed when we compared 40 undoubted cases of the Marfan syndrome and 40 controls matched for age, sex and race (2). The report of increased hydroxyproline excretion in the urine (3) is of interest because hydroxyproline is an amino acid unique to collagen. The promising preliminary observations suggest further investi-

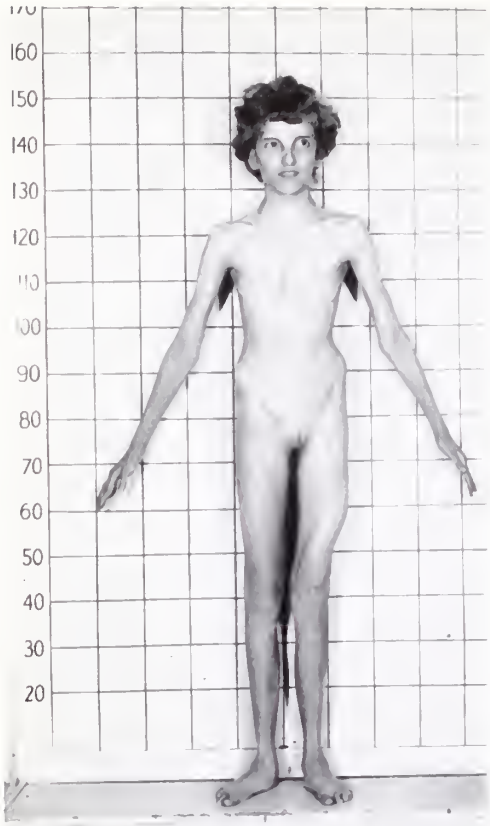

Fig. 1A.

Fig. 1B.

Fig. 1. *The Marfan Syndrome.* B. V. (948911), born in 1950, had at birth bilateral talipes equinovarus, dislocation of the left knee with extreme hypermobility of the joint, marked pectus excavatum, bifid uvula, tongue-tie, and strabismus. The feet were placed in casts. An umbilical hernia was repaired at 5 months. A reconstruction of the left knee was performed at 2 years. Strabismus was partially corrected at 3 years.

Beginning in the spring of 1960 she had four bouts of tachycardia. With the first the patient awoke startled and fearful with pounding heart. Pounding of the heart also occurred with running

Examination in 1960 revealed the skeletal features as referred to above and shown in the photographs. The lumbar spine showed a mild kyphos of a type unusual in the Marfan syndrome. No scoliosis was present. The ascending aorta was dilated on x-ray of the chest and an aortic diastolic murmur was heard. Blood pressure was normal in all 4 extremities. The patient wore thick lenses for correction of hyperopia. The fundus was visualized with an 8+ lens.

For sociologic reasons it has been impossible to investigate the family in full detail. However, one older sib is unaffected. The mother and several of her 9 sibs have eye trouble (strabismus, visual defect and in one cataract).

Despite the lack of ectopia lentis and the presence of hyperopia, not myopia, the diagnosis of the Marfan syndrome seems justified because of the characteristic skeletal and aortic changes.

In A are shown the skeletal features. Note the marked pectus excavatum. The patella on the left is high. The feet show rather characteristic eversion. In B is shown dilatation of the aorta. C is a spectral phonocardiogram recorded in the pulmonary area. In each cycle the second heart sound is followed by a diastolic murmur. The electrocardiogram in D shows a short PR interval and slurring of the QRS complex. These changes in a patient with paroxysmal tachycardia suggest either the Wolff-Parkinson-White syndrome or the syndrome described by Lown, Ganong and Levine: "The syndrome of short P-R interval, normal QRS complex and paroxysmal rapid heart action" (11).

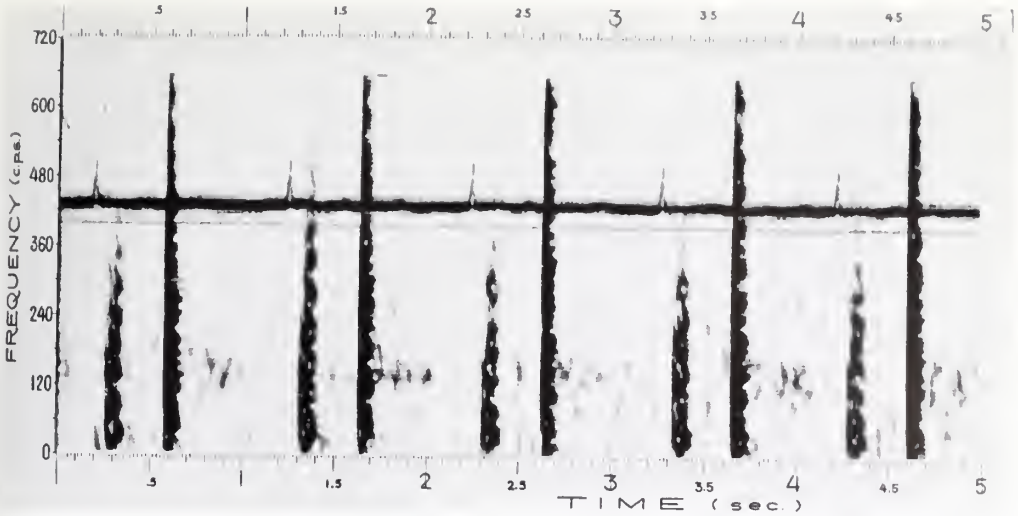

Fig. 1C.

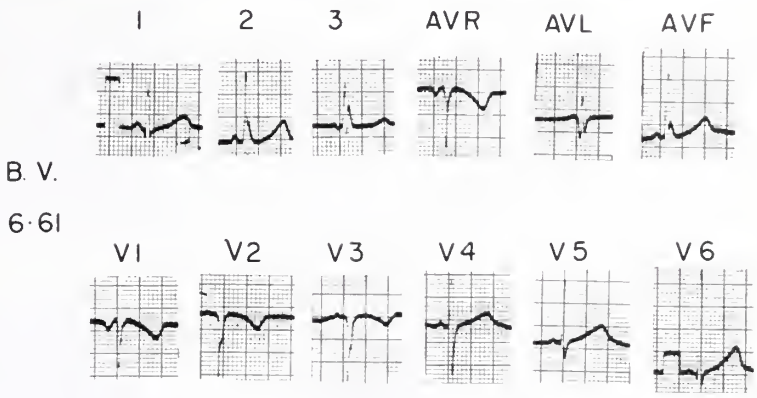

Fig. 1D.

gation of the matter. In the third place, last year it was reported that some but not all patients with the Marfan syndrome have giant satellites of certain chromosomes. From the work of my associates (4) I feel quite confident in saying that there is no causal relationship between giant satellites and the Marfan syndrome. Giant satellites represent an occasional morphologic variation in the karyotype comparable to a big nose and have by evidence now available no pathologic significance.

THE EHLERS-DANLOS SYNDROME

In the syndrome that goes by the name of Ehlers and of Danlos, leading manifestations are in the joints, which are excessively mobile, and in the skin, which is excessively stretchable, fragile and bruisable. Gaping skin wounds from minor trauma and a peculiar atrophic "cigarette paper" scarring characterizes the Ehlers-Danlos skin. Dehiscence of surgical wounds can be a troublesome problem. See Figures 4 and 5.

The best evidence on the nature of this disorder supports the suggestion that the defect concerns the way collagen fiber bundles are interwoven into a wickerwork. The basketry of collagen is excessively loose in the Ehlers-Danlos syndrome. The collagenous elements of the joint capsule, ligaments and tendons determine

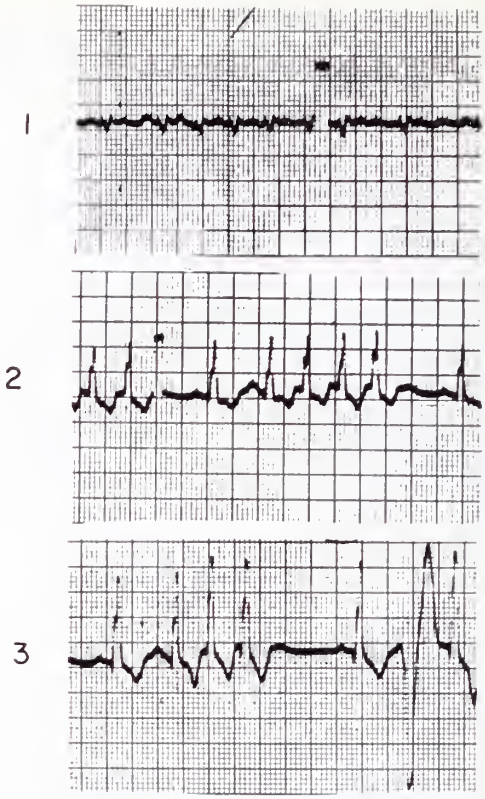

FIG. 2A.

FIG. 2. *The Marfan syndrome.* Electrocardiogram in M. C. (896200), who, like the patient in Figure 1, suffered from repeated bouts of tachycardia which was identified electrocardiographically as paroxysmal supraventricular tachycardia. The patient died at the age of 15 years during a bout of arrhythmia. Autopsy revealed that the mitral valve had five cusps which were thickened and nodular along the line of valve closure. Histologically this portion of the valve showed "basophilic degeneration." The chest x-ray and other information on this patient is provided elsewhere (Fig. 29, ref. 1). In A is shown runs of supraventricular tachycardia. In B, as in A, slurring of the QRS complexes is evident.

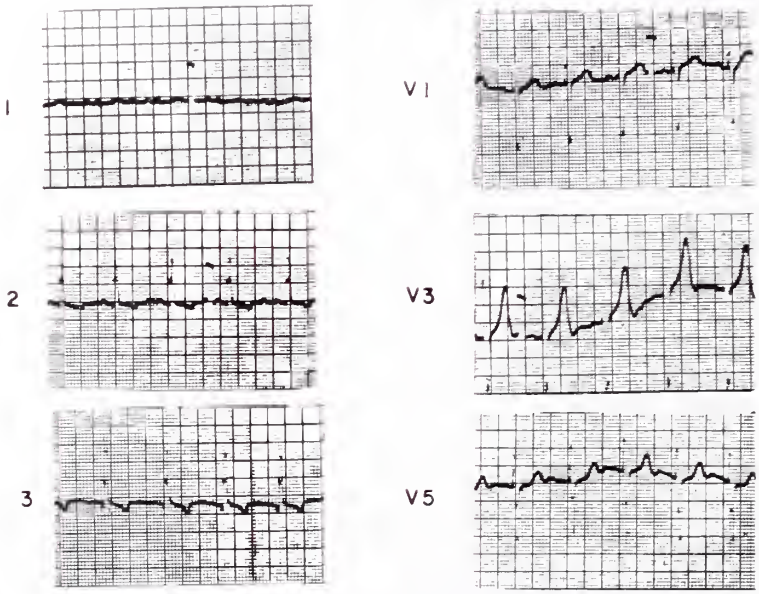

FIG. 2B.

how far a joint can be extended and the collagen elements of the corium determine how far the skin can be stretched. The seeming proliferation of the elastic fibers seen in some cases may be a phenomenon secondary to excessive stretching of the tissue, for I recall that in early observations on fibrogenesis in tissue culture Maximov and Bloom observed formation of elastic fibers mainly when the explants were placed under periodic stretch.

The most frequent internal manifestations are hiatal hernia and diverticula which may occur at any level in the gastrointestinal tract. Observations of diverticula and of the rare spontaneous rupture of the bowel which may occur in these cases come as no surprise if you recall that surgical "catgut" sutures are made from the serosa and submucosa of sheep and hog intestine. The collagen basketry is important to the integrity of the intestinal wall. Dissecting aneurysm of the aorta appears to occur also in the Ehlers-Danlos syndrome and there may be a specific type of cardiac involvement evident in some cases, but the information on both points is incomplete.

The Ehlers-Danlos syndrome is also inherited as an autosomal, that is, non-sex-linked dominant. It is frequently difficult to be certain of the diagnosis because loose-jointedness and stretchability of skin are graded characters. Of the five syndromes under discussion I have been able to assemble fewest families with the definite Ehlers-Danlos syndrome, but I suspect it is more frequent than this experience would suggest.

OSTEOGENESIS IMPERFECTA

Also known by the designation of fragilitas ossium and others, this is the most widely as well as the longest recognized of the heritable disorders of connective tissue, probably partly because it is one of the more frequent, and probably partly because of the dramatic occurrence of fracture with trivial trauma. It has been recognized for a long time that osteogenesis imperfecta is a systemic disease with abnormalities by no means limited to bone. The same defect in the organic matrix of bone, specifically the collagen, involves also the collagen of the skin, which is thin and scars peculiarly; of the tendons, ligaments and joint capsules, leading to loose-jointedness and a proneness to tendon rupture; and of the sclera, giving the thin "blue sclerotics," a familiar hallmark of the syndrome. Involvement of the osseous and soft connective tissue elements of the middle and inner ear in some way leads to progressive deafness, which in a current survey of our cases is found to be in some conductive, in some neural in type, in many mixed.

The gene for osteogenesis imperfecta has very wide expressivity, that is, the degree of severity is highly variable. At times it is so severe that multiple fractures occur in utero and the diagnosis can be made by x-ray before birth. In other cases there is very little except blue sclera and perhaps progressive deafness beginning in middle life.

Osteogenesis imperfecta is yet another single-gene-determined syndrome inherited as an autosomal dominant trait. There has been much discussion about whether the so-called congenital form of the disease in which multiple fractures occur in utero is different from the form with late onset of fractures and other signs. One must always be on the watch for heterogeneity in seemingly homogeneous genetic diseases, and the fifth syndrome to be discussed is an example of such heterogeneity. However, in osteogenesis imperfecta I have thought the evidence does not yet support unequivocally the possibility of heterogeneity. The congenital cases are, of course, very severe and they usually but not always come from normal parents. The isolated congenital cases have been thought to represent new dominant mutations. On rare occasion two offspring from ostensibly normal parents have had congenital osteogenesis imperfecta (Fig. 6). Such might suggest autosomal recessive inheritance. The questions of whether there is an increased rate of consanguinity among the parents of congenital cases and of just how frequent is the

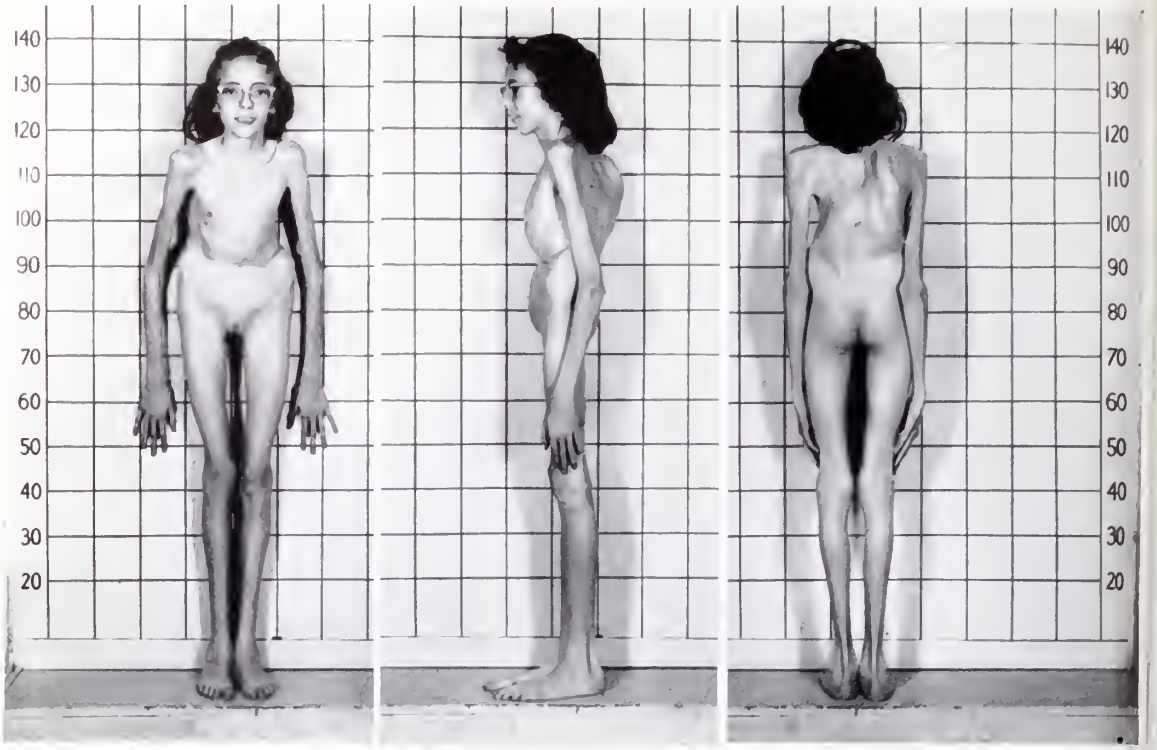

FIG. 3A. FIG. 3B. FIG. 3C.

FIG. 3. *The Marfan syndrome.* D. W. (663453), a white female born in 1949, is a sporadic case, probably a new dominant mutation. She had always been thin. Spinal curvature was noted at 18 months. At $4^2/_3$ years the diagnosis of the Marfan syndrome was made on the basis of dolichostenomelia, high palatal arch, subluxated lenses, and slight dilatation of the ascending aorta. At the age of 10 years an early diastolic murmur was discovered at the left sternal border. Phonocardiograms (D) revealed numerous clicks, presumably of extracardiac origin. A systolic murmur at the apex has been interpreted as that of mitral regurgitation. It is not certain that it is pansystolic (E). Its origin may be extracardiac. Because of progression in the scoliosis spinal surgery (fusion) was performed at the age of 11 years. Chest x-ray has shown progressive enlargement of the heart. The electrocardiogram has furthermore shown progressive changes of left ventricular hypertrophy and strain. The radiographic and EKG changes suggest that mitral regurgitation is indeed present.

A–C. Skeletal features.

D. Spectral phonocardiogram from left lower sternal border showing multiple systolic clicks of a type frequent in patients with the Marfan syndrome. The chest deformity, loose-jointedness involving the rib cage, and cardiac enlargement are probably factors operating singly or in combination in producing clicks of extracardiac origin.

E. Spectral phonocardiogram at the apex. The systolic murmur is mainly in mid and late systole suggesting extracardiac origin although EKG and X-ray finding support the diagnosis of mitral regurgitation.

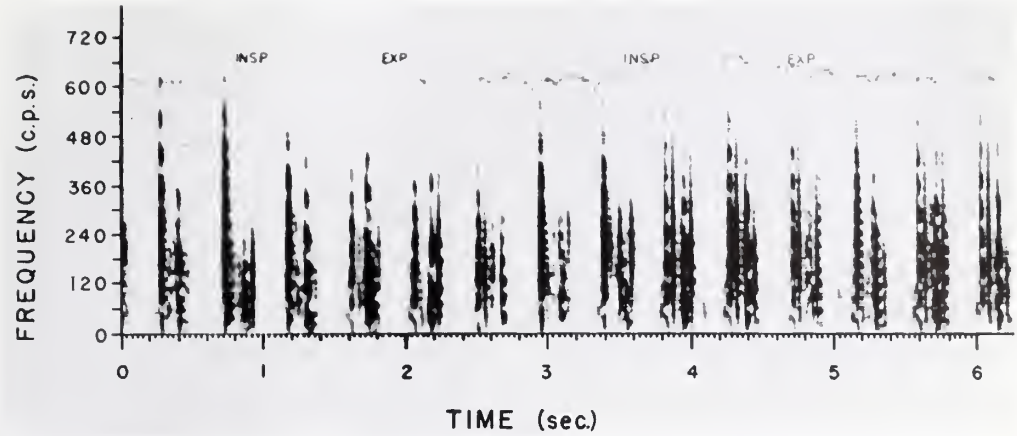
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FIG. 3D.

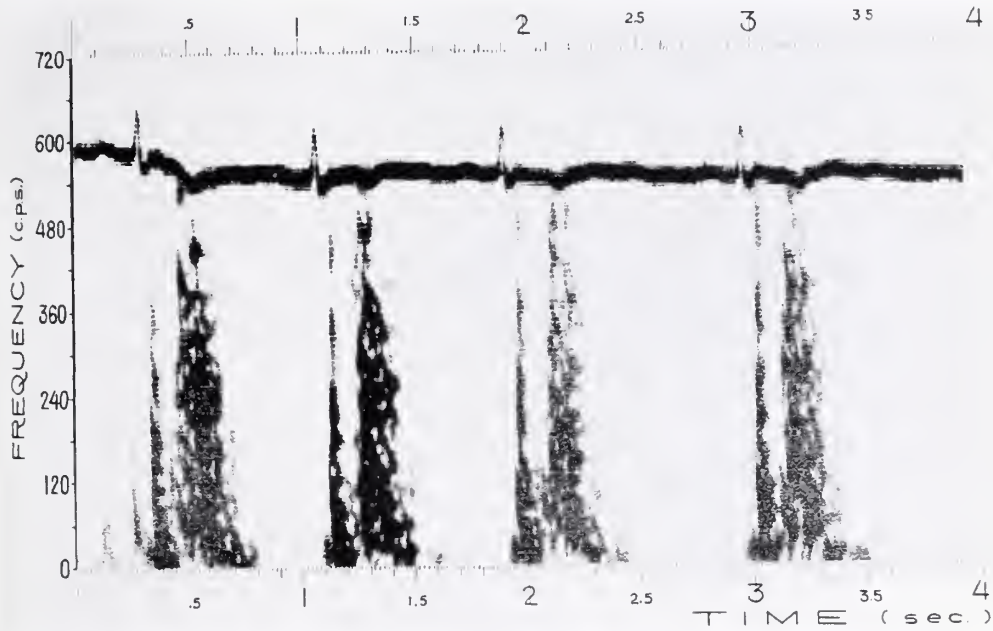
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FIG. 3E.

Fig. 4A.

Fig. 4B.

Fig. 4. *The Ehlers Danlos syndrome.* R. A. (911928), age 60 years, has all the typical features. No other member of his family is recognizably affected. Note the increased stretchability of the skin (A) as well as the peculiar scars indicating excessive fragility of the skin (A, B). Unusual facility in touching the tip of the nose (C) with the tip of the tongue is frequently present in this disorder.

Fig. 4C.

Fig. 5. *The Ehlers-Danlos syndrome.* Abnormal extensibility of the joints (A) and ears (B) are demonstrated in a 12-year-old boy. Fragility and bruisability of the skin are not present. Although rather few instances of this disorder have been reported in Negroes, the condition may not prove to be less common in this race than in Caucasians. (Courtesy of Dr. Glenn R. Stoult, Louisville, Ky.)

Fig. 5A.

Fig. 5B.

Fig. 6A.

Fig. 6B.

Fig. 6C

Fig. 6. *Osteogenesis imperfecta congenita in two offspring of ostensibly normal parents.* Shown here is the typical clinical and radiologic appearance of congenital osteogenesis imperfecta: Micromelia and multiple fractures are shown in the newborn views (A, B) and hydrocephalus which developed later is shown in C, a view at 10 months. The child died at the age of 13 months. A male sib with identical changes confirmed by x-rays and autopsy died at the age of 2 days. Two other sibs, ages 8 years and 8 months, are normal.

occurrence of more than one congenital case among the children of normal parents are being investigated, using the nation-wide register of cases being collected by the osteogenesis imperfecta foundation. At this point it appears that consanguinity is not increased and that multiple sibs are rarely affected.

PSEUDOXANTHOMA ELASTICUM

Pseudoxanthoma elasticum is a genetically conditioned degeneration of connective tissue elements of skin, eye and blood vessels. The neurologist Gowers invented the term abiotrophy to describe the behavior of hereditary states such as Friedreich's ataxia and Huntington's chorea in which the affected part is normal in early stages of life but nonetheless has an innate weakness leading to premature degeneration. The clinical behavior of pseudoxanthoma is that of an abiotrophy. Clinically and histologically normal skin, especially that subject to most wear-and-tear in flexural areas of the neck, axilla and groin undergoes deterioration, becoming redundant, grooved and nodular. This may occur in the first decade or not until the fourth or fifth decade of life. Cracking occurs in Bruch's membrane behind the retina producing angioid (vessel-like) streaks visible on fundoscopy. Finally degenerative changes occur in the wall of blood vessels, resulting in hemorrhage, especially gastrointestinal (Fig. 7), and in occlusive peripheral vascular disease.

Pseudoxanthoma elasticum is inherited as an autosomal recessive. Multiple sibs, the offspring of normal parents, are found to be affected in some instances and as a group the rate of consanguinity is increased in the parents.

It is a moot matter as to whether the element undergoing degeneration in pseudoxanthoma elasticum is collagen or elastin. I have been more convinced by the evidence suggesting that the change in this disorder is a form of elastotic degeneration of collagen, that is, that it is collagen that degenerates because of a genetic defect and that the degenerate collagen assumes some of the tinctorial and other properties of elastic tissue. Elastotic degeneration of collagen is well known after x-ray exposure and in senile skin (5). In vitro maltreatment of collagen can produce elastotic degeneration (6).

May I digress at this juncture to indicate what to my mind may be a fruitful approach to investigation of the basic defect in these disorders. The two most important recent ad-

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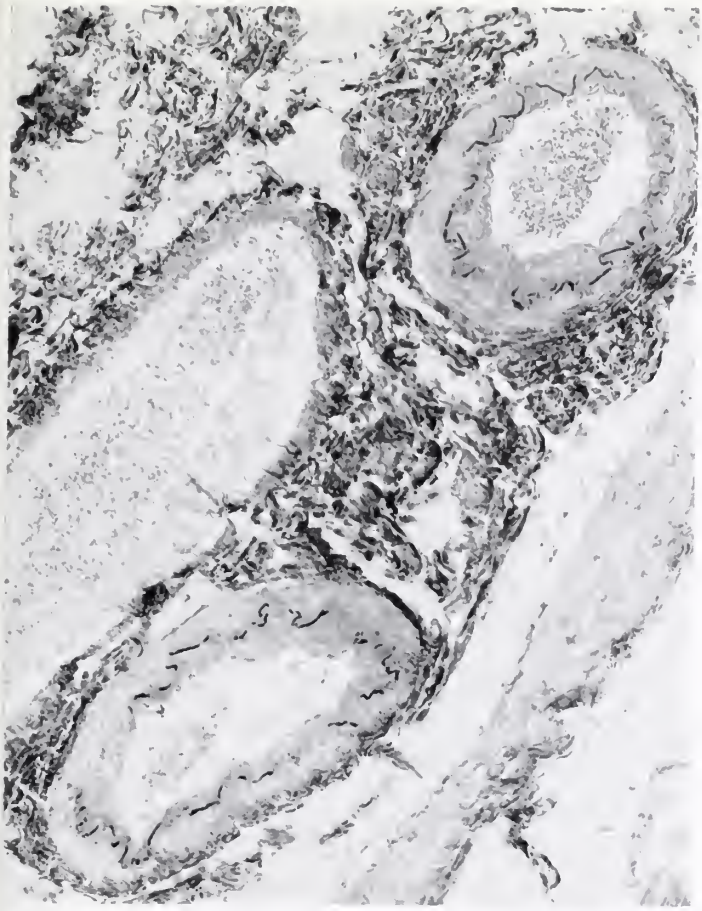
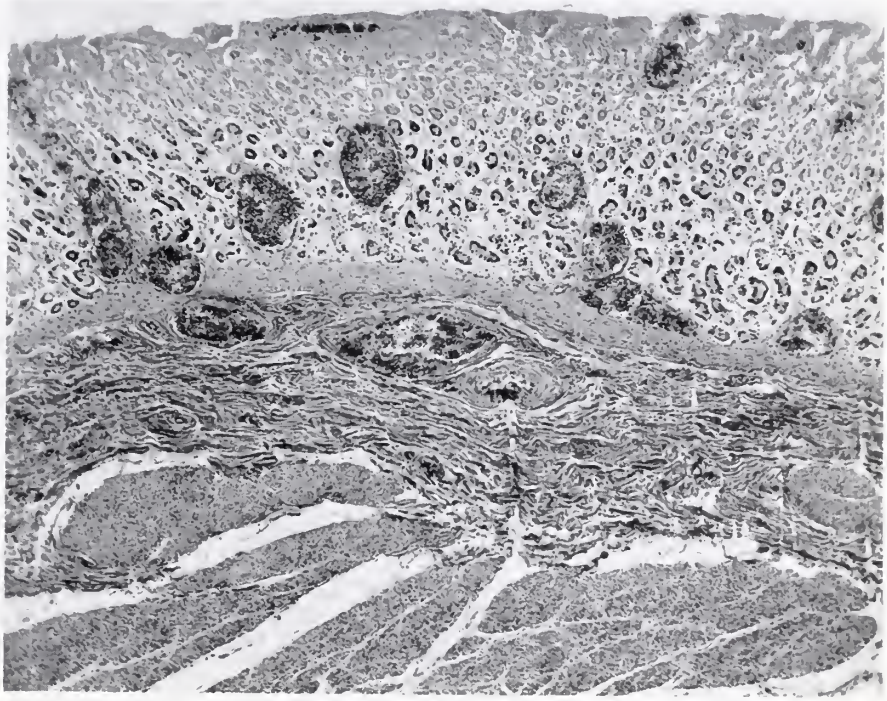
FIG. 7. *Pseudoxanthoma elasticum.* N. C. was 13 years old at death from gastrointestinal hemorrhage. Vomiting blood or passing blood in the stools had occurred repeatedly in the previous 6½ years necessitating 9 hospital admissions. Death occurred in 1945. The diagnosis was always in doubt clinically. At autopsy, too, no satisfactory diagnosis was arrived at. The diagnosis of PXE was made in a brother, now 36 years old, on the basis of typical skin and eye changes and a history of gastro-intestinal bleeding on one occasion at the age of 15 years. In retrospect, in the proband (N. C.) it was noted that on a hospital admission four years before death it was noted that "over cervical region is a raised pebbly eruption." Later it was noted that "over the neck, chest, abdomen and a small amount over the flexor surfaces of the arm there were elevated, small white papules some discrete, others confluent which appeared like scar tissue. This is similar to some skin conditions which she had previously." On one occasion the diagnosis of pseudoxanthoma elasticum was suggested by a dermatologist, along with other possibilities, but the total picture was not "put together." An ophthalmologist commented as follows: "The eye grounds are essentially negative. Over a broad area temporally from the fovea in both eyes there is a peculiar light brown mottling. The patient's brother is said to have this too and also the same sort of bleeding."

Histologic studies revealed astonishing focal or segmental vascular changes, especially in the stomach and small intestine, but also in many other organs, including heart, pancreas, kidney and to some extent in the brain. The changes were like those illustrated by Carlborg et al. (10). In some vessels there was fragmentation of the elastica and a deposit of collagenous material between it and the lumen, as well as loss of muscle (A). In the walls of some vessels there was material which in part stained brilliantly red with picro-Mallory like "fibrinoid." Mucosal vessels in the stomach and intestine were widely dilated and exceedingly thin-walled (B). The wall of the atrium showed dense "elastosis" of the endocardium (C and D).

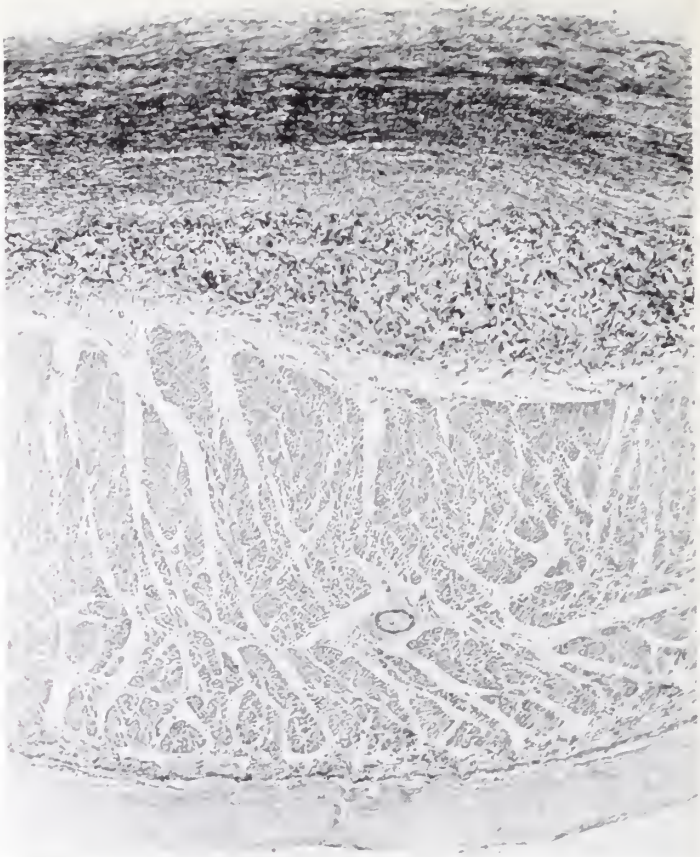


A. Vessels in wall of intestine. EVG. × 200.

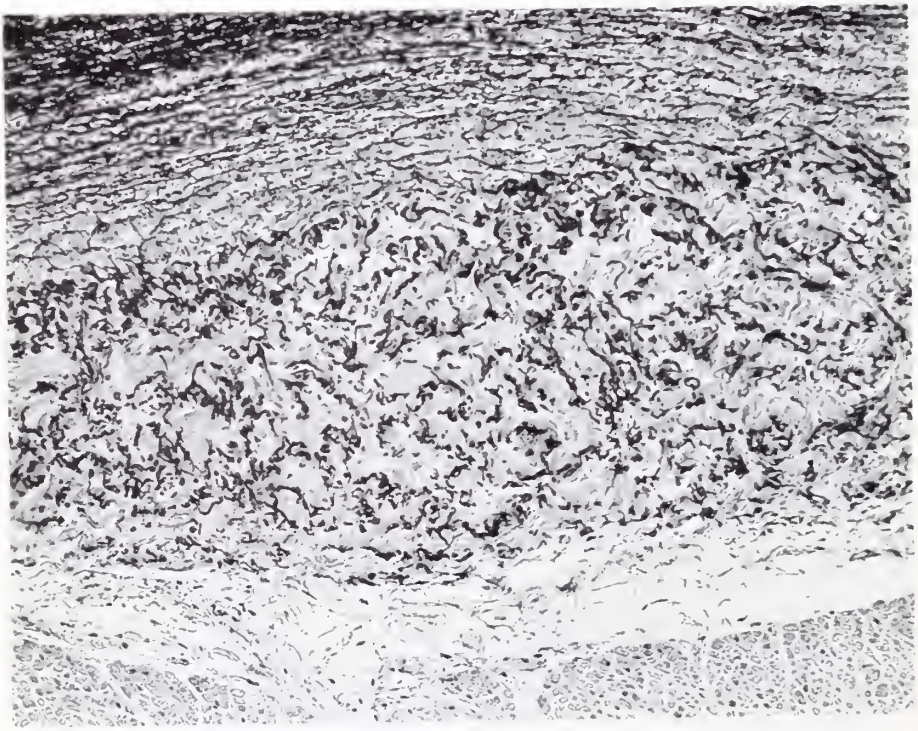
B. Stomach. N. & E., × 60.



C. Endocardium of right atrium. EVG. × 60.



D. Endocardium of right atrium. EVG. × 150.
(Courtesy of Dr. Averill A. Leibow, Professor of Pathology, Yale University School of Medicine.)



vances in medical genetics are 1) the discovery of the chromosomal basis of certain congenital abnormality of sex and soma and 2) the demonstration that a change in a single amino acid in a specific peptide is responsible for the abnormal physical properties of sickle hemoglobin and therefore for the manifestations of sickle cell anemia. The current dogma is that the gene specifies the amino acid sequence of proteins fairly directly. The protein so specified may be an enzyme or a protein of special function such as hemoglobin or conceivably a structural protein such as collagen. The previous "one-gene-one-enzyme" hypothesis becomes the "one-gene-one-polypeptide" or "one-cistron-one-polypeptide" dogma. The method of finger-printing provided the information on the change in sickle hemoglobin. The protein is digested into constituent peptide fragments and these are spread out in two dimensions by electrophoresis followed by chromatography. (The difference in sickle hemoglobin was found to be limited to one peptide arbitrarily called No. 4). When analyzed further it was found that in peptide 4 of sickle hemoglobin valine is substituted for glutamic acid.

It is quite plausible that a specific and unitary change in the amino acid sequence of collagen might result in changes in its physical properties responsible for the clinical picture in these syndromes. Fingerprinting of collagen is under way in several laboratories; the findings in these disease states will be well worth determining when the normal is adequately known.

THE HURLER SYNDROME

In the Hurler syndrome (also called gargoylism) there is good evidence that the fundamental defect involves mucopolysaccharide metabolism. Implicated are the mucopolysaccharide of cartilage leading to a characteristic skeletal deformity and dwarfism and the mucopolysaccharide of soft tissues leading to stiff joints. In 1952 the nature of Hurler's syndrome as mucopolysaccharidosis was proposed by Brante on the basis of evidence that the material deposited in the liver and spleen is not a lipid, as previously thought, but a mucopolysaccharide. In the next few years it became evident that there are two genetic varieties of gargoylism. In one form inherited as an autosomal recessive the disease is more severe and clouding of the cornea probably occurs in all cases. In the second, less frequent form the disease is milder, clouding of the cornea probably never occurs and most importantly the inheritance is sex-linked recessive precisely like hemophilia; that is, only males are affected and females transmit the trait. The third development in chronologic sequence was the demonstration that patients with gargoylism excrete relatively large amounts of mucopolysaccharide in the urine. Two are excreted, chondroitin sulfate B and what Karl Meyer calls heparitin sulfate. It was surprising to discover that there were no qualitative or quantitative differences in mucopolysaccharides excreted in the two genetic varieties of the disease. That two mucopolysaccharides are excreted suggests that the defect is located appreciably more proximal in a part of the metabolic chain common to the two.

The most recent development in this field is the discovery that a similar mucopolysaccharidosis occurs in cattle where it is responsible for a condition called "snorter dwarfism" (7). This veterinary disease should prove a valuable object of study.

Current research in medical genetics can perhaps be divided into four broadly overlapping areas:

1. Biochemical genetics concerns itself with the nature of the precise biochemical lesion in given hereditary disorders and with the chemical mechanisms by which the several manifestations of the basic lesion are produced.

2. Cytogenetics investigates the correlation between morphologic and numerical abnormalities of the chromosomes and congenital disease.

3. Statistical genetics is preoccupied with the proof of mode of inheritance, with ques-

tions of gene frequency and the factors altering it—mutation, selection, etc.—and with the analysis of pedigree data for genetic linkage.

4. Clinical genetics describes the range of phenotypic variability, seeks evidence of heterogeneity in seemingly homogeneous categories of hereditary disease, investigates the life-course of the disorder, attempts to influence phenotypic expresson of the gene by factors operating on the links connecting gene and phene, and looks for clues to the nature of the basic defect.

I hope I have indicated that all four approaches are being taken and must be taken in the elucidation of the heritable disorders of connective tissue.

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Management of the Chronic Mentally Ill[1]

By WILLIAM P. CAMP, M.D.[2]

SINCE the initial arrangements for this Symposium on "Management of the Chronic Mentally-Ill Patient" were made, there has been published a report so far-reaching in its implications for our topic that to fail to discuss it would be like ignoring the existence of the immune reaction when discussing communicable diseases. I am speaking of the report entitled, "Action for Mental Health", the work of the Joint Commission on Mental Health and Illness, just off the press.

I first quote a highly significant paragraph from that report: "Recommendation: No further state hospitals of more than 1000 beds should be built, and not one patient should be added to an existing mental hospital already housing 1000 or more patients. It is further recommended that all existing state hospitals of more than 1000 beds be gradually and progressively converted into centers for the long-term and combined care of chronic diseases, including mental illness. This conversion should be undertaken in the next ten years."

The report goes on to recommend that those "schizophrenic, involutional, geriatric and senile" patients who are found to be chronic be "transferred from the intensive treatment centers and placed in the proposed separate facilities for long-term chronic patients." It is further stated that many chronic patients get along with minimal supervision if the hospital is properly designed. This, as the authors point out, is a bold plan. I can see the thinking behind it but in certain aspects I believe it is dead wrong.

I like to say that I am not defensive about the greatly oversized mental hospital and its destiny. In fact, I would agree with the report that any hospital of over 1000 beds should have something done about it. My feeling is that it should be divided into smaller, workable units—each of which could have its own acute service, semi-acute and chronic services but with easy patient flow from one service to the other in both directions. This can be done; it has been done in Kansas at Topeka State Hospital, and in Iowa at the Institute of Clarinda.

The first danger I note in segregating the chronically ill is that, despite all fine words about rehabilitation to the contrary, these chronic institutions will inevitably become second rate. Physicians (and psychiatrists are no exception) do not find chronic disease a popular field. We want to see quick results and it cannot be denied that the drama of the acute illness and its course has real glamor for us. It is difficult, if not impossible, to build a professional training program around chronic illness, and we know that a treatment program without a live training program can quickly deteriorate. Our chronic patients obviously have just as much right to good care as our acute patients. If we are to have chronic mental disease hospitals we will have to learn more than we know now about how to motivate physicians. Do we dare to throw away the therapeutic zeal of the eager young psychiatric resident who does so much to help chronic patients before he learns from his elders that chronic patients cannot be helped?

Another more intrinsic disadvantage I see in the segregation of chronic cases is the directly adverse effect this practice has on both the chronic and acute patients. If one takes a series of admissions of chronic patients and sends them alternately to a back ward and an active treatment ward, one finds that at the end of the year almost all the chronic patients

[1] Panel discussion: other speakers included A. Victor Hansen, M.D., Henry R. Rollin, M.D., and William A. Steiger, M.D. Section on Public Health, Preventive and Industrial Medicine, 16 May 1961.

[2] Superintendent, Norristown State Hospital, Norristown, Pennsylvania.

sent to the back wards remain there and are indeed chronic whereas a goodly number of the supposedly chronic patients sent to the active ward have returned to the community in at least partial remission. The more active patients have obviously had a beneficial effect on the more chronic ones. The same is seen with senile admissions. Although at first glance it might seem humane and therapeutic to segregate the senile patients with others of their own age group in a relatively secluded area, we do such patients a disservice by doing so. It has been shown by experiments with a minimal stimulus environment that without an active background of noise, color, activity and movement, the individual tends to retreat from reality into fantasy, to withdraw and deteriorate. It works the other way too. We often see acute patients achieve a kind of serenity and increased self-esteem by having the opportunity to take in tow and minister to a more regressed chronic patient.

If chronic schizophrenia is a breakdown in communications, as John Cumming and others suggest, are we helping the patient when we place him permanently in a chronic area where no one communicates?

This is an age of increasing specialization of function and usually specialization does increase efficiency. But perhaps efficiency is not always a desideratum in the treatment of mental disease, acute or chronic.

The whole lesson of recent psychiatric advance, it seems to me, is that patients who were once thought untreatable are now treatable. The best future course appears, therefore, to be to blur, rather than sharpen, the lines between acute and chronic, "treatable" and "untreatable." What would have happened with the advent of chlorpromazine and reserpine if we had had all the chronically ill mental patients segregated in special hospitals and were treating them exclusively with the therapeutic milieu, activities therapies and rehabilitation programs? Without the constant and continuous pressure to get them out of the hospital, because of overcrowding, and without the impetus from enthusiastic young psychiatrists who were dealing with both acute and chronic patients at the same time, I seriously question whether we would have accomplished as much, and as fast, with the psychoactive drugs. I doubt whether we would have succeeded so quickly as we did in 1956 in reversing the inexorable upward trend of the figures for total hospital inpatients.

I do not wish to indicate that we can be complacent about the problems of chronic mental illness or that we are already doing all we can and should. The average age of our patient populations is increasing and, according to figures of the U. S. Department of Health, Education and Welfare, about 25% of our new admissions are 65 years of age or older. This tallies almost exactly with the figures at Norristown State Hospital. In most of these older patients the diagnosis is Cerebral Arteriosclerosis or Senile Brain Disease, each of which category is so far particularly frustrating from the standpoint of potential for recovery.

There are approaches to chronic mental illness which have positive value. For example:

1) The prevention of chronic incapacity of patients who are medically recovered by discharge-planning from the very first day of their hospitalization.

2) The use of day hospitals which entails less stigma and which enables the family to retain responsibility and to maintain contact and participate in the therapy of the chronically-ill patient.

3) The use of foster homes for aged patients to prevent the development of mental illness.

4) The use of "sitter" services for the aged to increase the tolerance of the family, to enable the family to take occasional weekend respites and vacations and thus prevent hospitalization.

5) The encouragement of outpatient psychiatric clinics to accept the chronically-ill, the expansion of such clinics and the development of transportation corps of volunteers—Wheels for Mental Health—to enable patients to reach these facilities.

6) The establishment of sheltered workshops.

7) A continuing program of education toward greater community involvement in the problems of mental illness, with increased use of untapped reserves of volunteer manpower.

8) The expansion of the Remotivation Program in existing hospitals. This is a highly-structured group therapy technique employing specially trained psychiatric aides. This technique, which has had considerable success around the country, is based on drawing chronic patients, at whatever level they may be, into discussion of nature, contemporary events, poetry and industry-without any conscious attempt to approach psychodynamics.

As the Report of the Joint Commission on Mental Health and Illness points out, all this will require flexibility in administration, admission and discharge criteria, and also probably some prepayment benefits or subsidy programs for the care of chronic patients.

The future does have certain grim aspects in the light of present-day knowledge, but I feel it is important to resist being stampeded into consignment of the mental patient—whom some might judge chronic—to some sort of non-medical limbo.

Therapeutic Use of Music in a Mental Hospital[1]

By HENRY R. ROLLIN, M.D., D.P.M.[2]

Musick is a roaring-meg against melancholy, to rear and revive the languishing soul: affecting not only the ears, but the very arteries, the vital and animal spirits, it erects the mind and makes it nimble.

Robert Burton (1577–1640), *Anatomy of Melancholy*

THE THEORIES designed to explain how music exercises its powers are many, and it is not proposed to add to them in this paper. Suffice it to say, however, that a primary disturbance in so much mental illness is in the field of the emotions. Schizophrenics, for example, who make up such a large proportion of the mental hospital population, suffer particularly in this respect. A characteristic of the disease, emotional flattening or an inability to respond appropriately in terms of feeling to a given situation, is often manifest. Again, among victims of affective disorders there is a morbid distortion of emotions ranging from elation or pathological happiness on the one hand, to melancholia or pathological unhappiness on the other. Indeed, one would be hard put to discover any form of mental illness, psychotic or neurotic, in which the emotions are not symptomatically involved. Music, it was felt, could be employed as a means whereby these emotional upsets could be attacked, either by stimulation or sedation, and the fundamental disease progress thereby mitigated. Let it be emphasized, however, that at no time was it considered possible that music could replace established methods of treatment such as electro-convulsive therapy, deep insulin therapy, leucotomy, psychotherapy, or chemical agents. From the beginning it was always considered that music, in the light of our present knowledge at any rate, could only be rated as an ancillary form of treatment, or perhaps as a catalyst, facilitating other therapeutic procedures. The sights were and still are kept low. Music therapy must still be regarded as an experimental project and modesty in its immediate aims in this, as in any other experiment, is not necessarily a handicap.

It is felt that the interests of this paper can best be served by giving a factual account of the work done in one hospital, Horton Hospital, Epsom, England, since the introduction of music therapy there in 1955.

There were no preconceived notions as to what the precise objectives should be or how the project with the aid of one music therapist employed for one day a week should be put into operation. (It should be interpolated here that there was then a "music appreciation program" in existence attended by all who cared to go, but it was felt that what must be done now should be more specific and individual.) There was no equipment except an antique piano salvaged from a ward and restored to its inferior best, and an electric phonograph. Initially, the only accommodation available was the Main Hall, built in the grand Victorian manner, large enough to house a fleet of mammoth aircraft, but with accoustics which had to be heard—or not heard—to be believed. But a start was made. To begin with, a group of male patients was selected who had had musical tuition either as professionals or as amateurs. It was felt on prima facie grounds that to reawaken an interest in an activity which at one time must have given deep satisfaction ought to be of therapeutic value. No attention was paid to the mental disease from which the patients

[1] Read at a panel discussion on "Management of the Chronic Mentally-Ill". Other panelists included William P. Camp, M.D., A. Victor Hansen, M.D., and William A. Steiger, M.D. Section on Public Health, Preventive and Industrial Medicine, 16 May 1961.

[2] Deputy Superintendent, Horton Hospital, Epsom, Surrey, England.

suffered or the phase of their illness. As by far the largest single clinical group in any mental hospital is that of schizophrenia, it is not surprising that of the nine patients who comprised the first group, eight were schizophrenics and one a manic-depressive. Of the nine, one had been a professional pianist of some standing; one had been a student at an academy of music at the time of his breakdown; another had been an amateur violinist of above average ability, and the rest had been pianists of widely differing levels of achievement.

The schedule at first was a simple one. After being assembled, phonograph records, initially selected by the therapist but later selected by the patients themselves, were played. Then the therapist played piano solos, mainly, as the program got under way, by request. Finally, each patient in turn was urged to play something—anything—at the piano. It must be remembered that not one of the patients had touched an instrument since admission to the hospital, which was for periods varying from several weeks to twenty years. The standard of performance, therefore, varied enormously from passing fair to excruciatingly bad. But virtuosity was not the objective; what was asked for and what was obtained, with a minimum or a maximum degree of cajolery and encouragement, was participation. It was heartening in these early days to see retarded and/or deteriorated patients scramble, some way at any rate, out of their psychosis and communicate by means of the music they played with their fellow men. That the communication was received was manifest in the applause of the rest of the patients for the performance, no matter how inferior it was. A group was formed spontaneously from individuals who by virtue of their mental illness tended to be solitary and asocial. It was the creation of this group, that is, an association of people with a common purpose and a common language, in this case music, which paved the way to future endeavors. Lest the one and only violinist be forgotten let it be said that he had his fiddle sent from home and that his contributions as a soloist, ductist, or in various small ensembles were greatly appreciated.

Some time later equivalent groups of female patients selected by the same criteria were formed and with a success no less than with the male groups. By early 1956 more than thirty patients had been included who had specifically asked to be so, or requests for their inclusion had been made by relatives. From these heterogeneous groups, a few patients, male and female, had crystallized out as being especially gifted, musically speaking, and to these, individual tuition was given.

In the summer of 1956 an important milestone was reached; a superb Steinway grand piano was acquired by an unusual example of Anglo-American cooperation. The long and benevolent arm of Madame Yolanda Mero-Irion, Executive Director of the Hospitalized Veterans Service of the Musicians Emergency Fund, Inc., in America, reached across the Atlantic and interceded on our behalf with Messrs. Steinway of London, so that the instrument was made available at a very special price which was paid by the Horton Management Committee. This was not only a symbol of success in that the Committee was sufficiently impressed with the experiment in music therapy to give its blessing in such a tangible form, but also as a boost to the morale of patients and staff alike. To play this magnificent instrument in preference to the antique model already described became a privilege, and there was competition between patients to be allowed to do so, either during music therapy sessions or during practice sessions which had by now been drawn up.

By now the number of patients handled had steadily increased, and as a further group activity, a women's choir had been formed. The standard of playing of the few patients for whom time had been found to give individual instruction had improved inordinately. Indeed, it was felt that the time was now ripe for concerts to be given by the patients for the patients. These were started in the spring of 1956. The programs were

ambitious, and, considering the material with which the music therapist had to work, the fact that they were performed at all, at any level, was in itself an achievement. Some of the performances were extremely good. Perfection was not aimed for and certainly not attained; but what was achieved was a psychological triumph for performers and audience alike. The frequent rehearsals had welded the performers into a large group with the same group and individual tensions and anxieties which normal musical groups undergo in similar circumstances. The fillip to their egos once they had done their bit was all too obvious. They glowed with pride as they took their bows and again when they received their little gifts as tokens of appreciation of their efforts. Temporarily, at any rate, they had fulfilled man's fundamental need—to be needed. The mentally ill, admitted perforce to a mental hospital, are for the length of their stay failures. They have failed their social group, their families, and particularly themselves. What better index of hope for the future could there be than to stand in the limelight, in both the literal and metaphorical sense, to receive the plaudits of their fellows? For the audience, composed of over three hundred patients, shared in the success of the concerts and reflected glory of the performers, and in so doing they too became part of the group—the music therapy group—in just the same way as a school, a university, or a whole town can project themselves into, and identify themselves with, the triumph of their team. As further evidence of this phenomenon it should be mentioned that these patients' concerts occasion much more discussion for a much longer time than any given by outside artists, no matter how eminent.

Having established these musically-orientated groups it was felt that the net could be cast wider and experimental groups started with patients to whom music, or rather rhythm, might appeal at a more primitive level. To this end, in March 1957, percussion bands were formed with, as the stock of instruments gradually increased, drums, tambourines, triangles, cymbals, bells, maracas, tambours, chime bars, trumpets and "nightingales." The criterion for inclusion in these groups was that no other form of treatment had been able to hold their interest. Clinically, therefore, they constituted the least hopeful element in the hospital. The technique was quite simple; the piano was played with a forceful rhythm, usually incidentally by another patient, while the patients in the group were encouraged by members of the staff to shake or beat the percussion instruments which had been handed to them. These instruments require no musical skill whatever; all that is needed is to determine and maintain the rhythm of the piano. The result is not nearly as cacophonous as might be expected in spite of, or because of, the limitations in tonal range. In fact, with a percussion band going full blast, and this is the desired result, the effect can be very stirring. The regressed schizophrenics who make up most of these groups are by the nature of their psychosis withdrawn, apathetic, and anergic, so that spontaneous participation was not expected nor achieved. However, with coaxing and encouragement, the majority of the patients were induced to play their part, or their instrument, at first feebly, but later with growing gusto. The success of the venture could be measured quite simply indeed by the volume of sound which emerges from the group, and in this respect a decibel recording instrument is not needed; an arbitrary assessment can be made from the distance from the music room before the group can be heard—or from the volume of complaint from neighboring departments or offices! There can be no doubt that these percussion groups have succeeded within the limited objectives set for them. It is most reassuring to see these lost, preoccupied beings become, for the moment at any rate, animated and "have a go" with whatever instrument they happen to wield.

In July 1957, a second, important milestone was reached; the acquisition of a music room. In keeping with the other assembly halls at Horton the chapel is of giant proportions, far

too large for the spiritual needs of the community, patients, and staff. With the kind cooperation of the Management Committee and the ecclesiastical authorities, permission was obtained to annex roughly a quarter of the chapel as a music room and concert hall. At the moment there is only a symbolic wall separating the spiritual from the secular in the form of a series of screens most attractively painted by a patient who is a member of one of the music therapy groups. Plans are in hand for a real conversion whereby the music room will become self-contained.

The acquisition of a home of its own gave the music therapy project a decided fillip. New experimental schemes were set in motion and yet another group, a recorder group with mouth organ and/or banjo and autoharp plus a percussion section accompanied at the piano by a patient, was formed and has proved a great favorite. Indeed, so great were the patients' demands for practice time, either for individual patients or small ensembles, at times other than the official music therapy sessions, that a year or so ago a second music room was fashioned from a disused general bathroom, and two reasonable upright pianos housed there. It is hoped, when funds become available, to repair and redecorate the room which, despite its present state of dilapidation, is in full use. Practice lists for both music rooms have now to be worked out in advance so that there is no clash of times or interests.

A complicated organism such as a mental hospital is never static. The turnover at Horton is substantially more than 1,000 patients a year. Among them are individuals who during their stay because of their special talents can be incorporated into the music therapy program, which has always been kept sufficiently elastic to allow for considerable modifications. At the time of writing, for example, there is a male patient of 32 under treatment for obsessive-compulsive neurosis. He has had professional training as a composer and conductor. He has not only organized and trained a mixed chorus—mixed in terms of sex and clinical conditions—to a laudable degree of efficiency, but has written arrangements of popular songs to suit his unorthodox group in addition to composing works of his own for it.

It would be pertinent to add a note concerning the attitude of the nursing staff to the project. To begin with there was an understandable scepticism which gave way as the scheme got under way, and particularly after the most successful patients' concerts already referred to, to growing enthusiasm and increasing cooperation. Nowadays there are up to eight members of the nursing staff, male and female, present during the sessions, and their help is particularly valuable with the percussion groups where so much encouragement and coaxing is needed to ensure the patients' participation in the activity. It is noteworthy, too, that two male recruits to the nursing staff, both of whom have had musical training, came to Horton because of its music therapy program. Their help in carrying on the work, particularly with the ensembles, in the absence of the music therapist has been most valuable. Furthermore, the interest and cooperation of the Occupation Therapy Department is now wholehearted, and attendance at the groups is considered as an integral part of the training of student occupational therapists at the hospital.

Today, as a result of the marriage between the occupational therapy and music therapy departments percussion-band sessions are held as a regular feature of the former's program for its chronic patients and are directed by one of its own staff.

As offshoots to the main program, mention should be made of some minor experimental projects, not necessarily successful but all showing the growing interest in music as a therapeutic agent and a certain spirit of adventure in putting it to use. Thus, in 1958, at the suggestion of a member of the nursing staff, music on phonograph records was played in the Insulin Therapy Ward at the time when the patients were emerging from coma. During this period of half-consciousness, patients are very often restless, irritable and confused. Music does seem to allay the restlessness in

some cases, due partly to the sedative effect of the music itself but also to the establishment of contact with reality through the auditory stimulus provided.

One of the most satisfactory and satisfying developments in the use of music, and one on which increasing emphasis has been placed recently, is in the geriatric wards. The number of patients in Horton over the age of 65 is at the moment 148 male and 396 female, i.e. 38% of the total patient population. Inherent in the problem of treating the aged, no matter what the individual psychopathology may be, is how to combat boredom. To this end music has been used in a variety of ways. At the suggestion of the nursing staff "keep fit" classes have been held, admittedly of a very simple kind. In these movement and relaxation to the accompaniment of phonograph records are encouraged. A year or so ago under the aegis of the music therapist a percussion band was formed which has gone from strength to strength, or rather from volume to volume. Perhaps the most popular of all the activities is the weekly concert cum dance. In this session, live music is provided by members of the regular music therapy classes to a mixed group of 60–70 old people who foregather in a large female ward. The afternoon's program consists of musical items provided by individuals and groups, all designed so that the old folk can join in choruses, add their quota of sound with percussion instruments which are handed round, or merely clap their hands or stamp their feet to the rhythm. After a communal tea an impromptu dance is held during which the Derbys and the Joans take the floor either spontaneously or with encouragement from the staff. Here again, what is asked for and what is obtained is participation of a surprising degree. That the entertainment is enjoyed is manifest in the party spirit which abounds, the applause for the entertainers and the degree to which both sexes "dress up" for the occasion.

In the account given of the growth and development of music therapy in this hospital, no attempt has been made to assess the improvement, either individually or collectively, which has resulted. This is because six years of experience have strengthened the belief that music is not, and is never likely to be, a primary form of treatment in mental illness. However, as an ancillary, or, perhaps, catalytic form of treatment there is no doubt that music plays its part, and an important part at that. As witness to this claim it should be restated that during the time in which music therapy has been practiced, the enthusiasm of the patients for this particular activity, either on a group or an individual basis has progressively increased. The whole project has snowballed. A music therapist is now engaged on two whole days a week, but subsidiary programs are conducted by members of the nursing and occupational therapy staffs on almost every day of the week. The numbers handled directly have increased enormously since its inception and there is an increasing diversity of activities during the actual classes. It is appreciated that these claims, modest as they are, would not stand up to strict scientific enquiry, but if opportunity in the shape of further money and personnel to establish a controlled experiment were provided, then data of a more acceptable "scientific" sort might be forthcoming. Nevertheless, there are several specific cases where the improvement manifested, leading to their discharge or to their upgrading within the social structure of the hospital, was, on clinical grounds, attributable to their participation in music therapy.

Case Reports

Case 1. Mrs. E. H., age twenty-three on admission as a certified patient in September, 1952. The diagnosis was schizophrenia; she was deluded and hallucinated for hearing, i.e., she believed she was being persecuted by the police, that her thoughts were being read, and that she was being plagued by "bangings and rappings." Under the influence of these phenomena her behavior was at times grossly disturbed. She was treated with deep-insulin and electro-shock therapy from October, 1952, until November, 1955, and although her

condition underwent fluctuations it was, even at best, far from satisfactory. She was argumentative, quarrelsome, and at times violent.

She was, by virtue of her musical training in her native Bulgaria, included in the first group of female patients selected for music therapy which began in November, 1955, i.e., after physical methods of treatment had ceased. Despite the fact that, as a girl, she must have achieved a relatively high standard of performance as a pianist, she had not touched a piano for years. However, she was encouraged to play, which she did reluctantly, but on the strength of her performance she was selected for individual treatment. The early stages of her musical rehabilitation were far from easy because of the potency of her psychotic symptoms. Gradually her dexterity returned and she applied herself with increasing zest to her practice. As she did so, there was a perceptible falling away of the strength of her delusions and hallucinations so that, at least, she was able to live with them.

She was one of the soloists in the three first patients' concerts and although she needed a great deal of support and encouragement to take her place on the platform, when she did so, she performed admirably.

In the summer of 1957, her behavior, in spite of the persistence of symptoms, had so improved that she took a job as a salesgirl in the town while continuing to live in the hospital. Finally, at the end of July, 1957, she was discharged from the hospital and has managed to maintain herself on her own in London ever since.

Case 2. Mr. G. W., age twenty-seven on admission as a voluntary patient in August, 1952. The diagnosis was schizophrenia; symptoms had been present for at least four years prior to admission and in other hospitals he had had physical methods of treatment.

He was a serious behavior problem to begin with; he was lazy, dirty, and totally unreliable. Thus, he would abscond from the hospital, go into the town, and would be returned by the police for a variety of misdemeanors which included begging, theft, and indecent exposure. Because of this total unreliability, he had to be kept in a closed ward.

He had had a sound musical education and had been a reasonably accomplished pianist. Because of this background, he was one of the original male group selected for music therapy in October, 1955, and later for individual treatment. His piano playing has improved enormously and he is now, and has been for some years, the cornerstone of the various small ensembles which have come and gone. He is an excellent accompanist and, for example, accompanied Mrs. E. H. in the concerti arranged for two pianos given at the patients' concerts.

As his interest and proficiency in his music rose so his status vis-a-vis his fellow patients rose too. Gradually, he was given more and more privileges and for some time now he has gone home regularly for week-ends. He is neat in his appearance and conducts himself with propriety.

Case 3. Mr. C. S., age seventy-two on admission as a voluntary patient in January, 1956. He was a case of chronic hypomania; garrulous, overactive and grandiose in manner.

He had been a good amateur violinist in his native Germany, but had neglected his instrument for some years. He was selected for inclusion in the early groups for music therapy and volunteered to have his fiddle brought from home. He was encouraged to practice and ultimately played in various ensembles and was a regular performer in the patients' concerts until his death in 1960.

The symptoms he originally exhibited remained, but his social behavior, after his interest in music was reawakened, was so improved that he was able to enjoy all the privileges available in the hospital.

Case 4. Mr. F. M., age fifty on admission in October, 1958. The diagnosis was chronic alcoholism.

He is a professional violinist who in the past held important jobs as a leader of various light orchestras. As his alcoholism increased he slid down the social and professional scale until he became unemployable. He finally pawned his

violin. When admitted he was penniless, destitute, with his morale broken.

He was placed in one of the music therapy groups. Reluctantly at first, he agreed to play on a borrowed fiddle to the group. Gradually, his confidence and proficiency improved and every facility was given him to practice outside music therapy sessions. Eventually, a loan was arranged so that he could redeem his own instrument from pawn. He was, not unnaturally, overjoyed to be reunited with it and redoubled his efforts to regain his old proficiency. In mid-December he was successfully auditioned for a job as a leader of a ship's orchestra and left to take up his appointment two weeks later.

Thomas G. Morton and Blood Transfusion: 1869-1878[1]

By WILLIAM D. SHARPE, M.D.[2]

THOMAS GEORGE MORTON was born in Philadelphia in 1835 and died at his summer home in Cape May, New Jersey, in 1903. He was graduated in medicine at the University of Pennsylvania in 1856, and served as Resident Physician at Pennsylvania Hospital for the customary two year term. From 1860 until 1864, he served as pathologist to the hospital, and after 1864 was one of its surgeons, remaining connected with "Old Pennsylvania" all his professional life. He was a Fellow of the College of Physicians of Philadelphia and held many teaching, attending and consulting appointments in the city's hospitals throughout his life. During the War Between the States, he served as an assistant surgeon in various Federal Military Hospitals in the area, and was most actively involved on the surgical service of Dr. D. Hayes Agnew at Chestnut Hill (1).

Dr. Morton liked to teach: his clinical sessions in the amphitheatre at Pennsylvania Hospital were attended by almost a generation of students from the University of Pennsylvania and Jefferson Medical College, and enough holograph reports of these lectures have survived in the hospital library to document the calibre of his practice and the careful preparation of his conferences. He was an original and, for the time, a daring operator, including ophthalmology and orthopedic surgery within his competence. He is assigned priority for the correct diagnosis of and successful laparotomy for acute appendicitis on 27 April 1887 (2). He was influential in introducing the new concepts and techniques of antiseptic surgery to Pennsylvania Hospital and to Philadelphia. In more mature years, he interested himself in the history of medicine, (3) and an unusually well developed social consciousness manifested itself not only through his years of service to his hospital and a heavy load of charitable work and consultations, but through eleven years' service to the Commonwealth of Pennsylvania as its Commissioner of Public Charities. Kelly and Burrage's brief biographical note mentions his work on blood transfusion during the eighth decade of the nineteenth century, but this is overlooked in most of the standard accounts of this subject. Enough material has survived to permit a review of his experimental and clinical trial of blood transfusion.

I

The development of blood transfusion as a useful clinical technique depended upon an extension of intravenous injection of medicinal substances to include blood, upon animal experimentation to develop practical methods and upon the use of transfusion on rational grounds after careful diagnosis and with a reasonably correct understanding of disease processes for which transfusion of blood might offer amelioration. Anecdotes derived from Ovid's *Metamorphoses* or apocryphal accounts of the misadventures of this or that elderly Renaissance ecclesiastic do not pertain to the development of modern techniques of blood transfusion. There are scattered reports of transfusion in medical literature prior to the middle of the seventeenth century, but it is difficult to ascertain whether these refer to speculative or to actual events. Since these early efforts seem often to have been based on belief in some mystical or magical efficacy of blood itself rather than upon sound physiol-

[1] Read before the Section on Medical History, College of Physicians of Philadelphia, 18 April 1961.

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ogy, they cannot be considered transfusions in any modern sense of the word (4).

Giovanni Francesco Colle (1558–1631) definitely describes blood transfusion in 1628, and Johann Sigmund Elsholtz (1623–1688) discusses the intravenous infusion of drugs, including blood, in his *Clysmatica nova* in 1665, a work better known through a Latin translation published two years later. In 1657, Sir Christopher Wren (1632–1723) and, in 1665, Robert Boyle (1627–1691) injected dissolved substances into the veins of living animals without actually killing them. In February 1665, Richard Lower (1631–1691), of Oxford, transfused blood from the cervical artery of one dog to the jugular vein of another, with survival of both animals (5). On 23 November 1667, Lower transfused a fifteen year old boy with nine ounces (270 ml. ±) of lamb's blood, a procedure attended by no mishap other than the boy's reporting that he had felt "a very great heat along his arm." This must be considered the first reported blood transfusion to a human being in the English-speaking world.

The first severe transfusion reaction in a human being seems to have occurred in Paris in 1667, when on 15 June, John Baptist Denis (?–1704) reported to the Royal Society that a transfusion of twenty ounces (600 ml. ±) of lamb's blood to a human being was followed by severe pain at the injection site, a rapid and irregular pulse, sweating, pains in the back and flanks, vomiting, diarrhea and several days of melanuria. The transfusion was not repeated and the patient survived. In 1668, Dr. Denis was less fortunate: a patient received his third transfusion of animal blood and forthwith died. The resulting lawsuit by his understandably aggrieved widow seems to have been the first case of litigation arising from a transfusion mishap. The Faculty of Medicine at Paris soon forbade the procedure, but nevertheless the possibility of transfusion of blood became widely enough known to be mentioned in many standard textbooks from that time downward, although there is no evidence that the method was ever very extensively used in practice.

Transfusion apparently fell into disuse until James Blundell (1790–1877), a London physiologist-obstetrician of considerable practice—whose estate at his death was worth £350,000—revived blood transfusion as a possible remedy for the problem of severe post partum hemorrhage, a frequent and serious complication in pelves affected by rickets and tuberculosis following aggressive use of mid- and high forceps at a time when survival after cesarean section was a reportable medical curiosity. Blundell used a variety of techniques in his experiments with dogs, and depended most heavily upon a cannula directly connecting donor to recipient, or a brass syringe which held eleven drams (44 ml. ±) of undefibrinated blood, and which was used for rapid direct transfusion. A more elaborate apparatus involving a collecting funnel which fed blood into a piston-chamber for injection through a three-way stopcock was abandoned because of difficulty with clot formation. He was most successful with a simple funnel, tube and canula apparatus which administered blood by gravity flow, much like the intravenous infusion sets used in American hospitals up to and including the second World War. He concluded that venous blood was as useful as arterial; that a moderate intravenous air injection—20 ml. or less—need not be fatal; that replacement of only a fraction of the total blood loss would usually suffice to save life if transfusion were to be helpful at all; and that transfusion of blood from one animal species to another was so dangerous as to be impracticable (6).

In 1818, Blundell reported his first successful transfusion in a patient with carcinoma of the stomach: twelve ounces of whole blood (360 ml. ±) were given by the syringe and cannula technique, and although the patient felt subjectively better after the transfusion, he died of his disease fifty-six hours later. Transfusion was performed by Blundell eleven times, using between four and sixteen ounces (120 ml. ±–480 ml. ±) of blood without defibrination or anticoagulation: excluding two patients already dead and one dying of

malignant disease, eight cases are left with five recoveries. Blundell's work aroused wide interest and not inconsiderable controversy: the first issue of *The Boston Medical and Surgical Journal* contains a review of his work, (7) and the 1834 edition of his popular textbook of obstetrics reviews his conclusions on the indications and techniques for blood transfusion in cases of postpartum hemorrhage (8).

John Louis Prevost (1790–1850) and J. B. A. Dumas (1800–1884) were successful in using defibrinated blood for animal transfusions, and this seems to have been the first successful attempt to preclude clotting during transfusion. Though widely considered a complication by those performing these early blood transfusions, the tendency of blood to clot may have saved lives through preventing severe transfusion reactions but this is by no means certain. Severe transfusion reactions are carefully described but were usually ascribed to clots, bubbles or some overwhelming insult to the "nerve force." Pains were taken to keep the blood transfused free of clots and bubbles, and almost without exception, blood was used within minutes of its withdrawal. The syringes and receiving bowls were warmed—100°F. (38°C. ±) was thought to be the optimum temperature and with the crude clinical thermometers then available, this was probably a safe approximation to body temperature. The British obstetrician J. Braxton Hicks (1825–1897) used sodium phosphate solution mixed with four times its volume of blood as an anticoagulant, but three transfusions reported in 1868 using Blundell's gravity drip were unsuccessful (9).

By the middle of the nineteenth century, attempts at transfusion with human blood were chiefly in British hands, largely for postpartum hemorrhage. Continental workers still applied themselves to transfusions of animal blood to human beings, and there is little substantial evidence for American work on this problem very much before Morton's time. Perhaps this may be explained by expanding frontiers, the generally low status of American medical education at the time and such, but in fact, the most popular medical journals of the day—*The Medical Record*, *The American Journal of the Medical Sciences*, or *The Boston Medical and Surgical Journal*—provided not only the dire prophecies about the future of medicine, sweeping denunciations of current medical education and lamentation concerning the economic plight of the private practitioner which editorial Nestors have maintained like so many Aristophanic frogs, but remarkably prompt and full reports of foreign work, case reports, "clinical lectures" and thoughtful essays correlating medical practice with current advances in basic medical sciences. American physicians of the nineteenth century had ample means whereby they could be informed of medical progress.

Over and above postpartum hemorrhage, blood transfusion was occasionally applied in other conditions, chiefly those marked by abnormal bleeding and anemias which proved refractory to accepted therapy. Thomas Smith, in London, had treated hemorrhagic disease of the newborn with blood defibrinated by beating the blood up with an egg-beater and straining it to remove the clot. In 1873, he reported temporary improvement following an eleven ounce (330 ml. ±) transfusion in an eight year old girl nearly exsanguinated by epistaxes due to purpura: though the patient died a few hours later, Smith felt that she had gained an hour or two of life (10).

Though blood transfusion does not play a part in the official medical accounts of the War Between the States, as early as 1869—the year of Morton's first reported transfusion—Joseph Buchser, of New York, reported the successful transfusion of three ounces (90 ml. ±) of blood mixed with a solution of carbonate of soda as an anticoagulant (two grains to two drams of water—about 2% w/v). The patient was a twenty-eight year old woman suffering from epistaxis, hematuria and purpura following typhus. She was apparently dying at the time of transfusion and, except for a troublesome postoperative thrombophlebitis, she made a good recovery (11). It is significant that one of the writer's objections

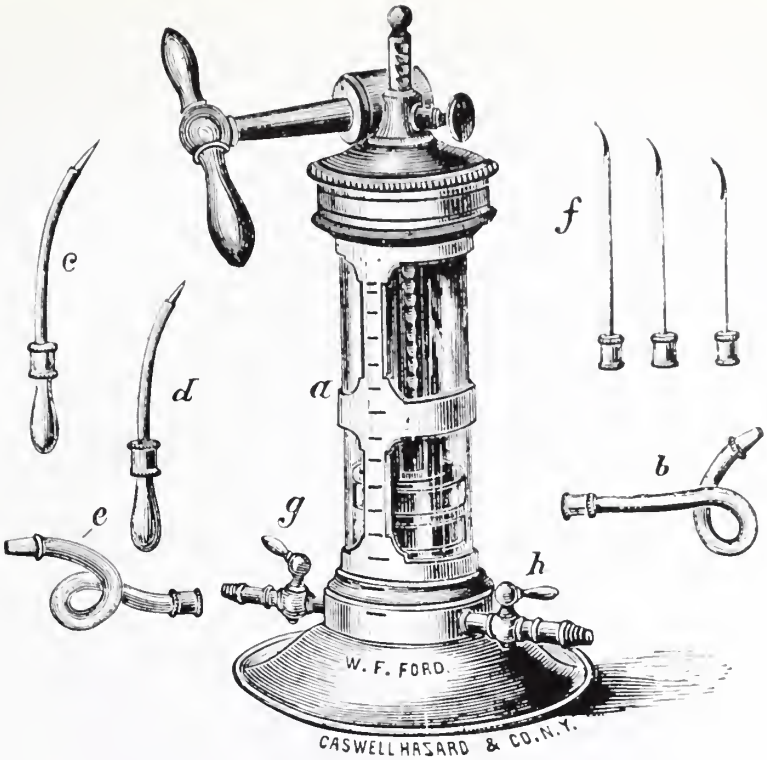
Aveling's Apparatus

to transfusion by the syringe and canula technique was the prohibitively high cost of the syringe: $80.00 at a time when the buying power of the dollar was at least ten times what it is today.

Back in London, J. H. Aveling (1828–1892) reintroduced blood transfusion and undertook experimental work in 1863; by 1873 he had perfected his apparatus, a simple gum rubber tube easily adapted to carrying in the physician's pocket. It had an oval bulb in the center and a cannula at each end—pressure on the bulb set up a pumping action to move blood from the donor to the recipient. To avoid injection of air, it was filled with warm water before use (12). Aveling was chiefly concerned with postpartum hemorrhage, and his work was widely reported in the United States, with many attempts at modification. The American Medical Association met in Detroit in 1874, and Aveling's apparatus was discussed by the Section on Obstetrics and Diseases of Women and Children on 2 June 1874: most of those present, including J. Marion Sims, felt that while an interesting possibility, transfusion had not been successfully done in the United States for post partum hemorrhage (13).

Blood transfusion was discussed at several meetings of physicians in New York in 1874: Blundell's work seems to have been better known than Aveling's. Austin Flint, Jr., reported a seven ounce (210 ml. ±) transfusion in New Orleans during the winter of 1860–1861, with the patient surviving twenty-four hours. The consensus was that blood transfusion was a highly dangerous procedure to be used only in cases of desperate illness, that small quantities of blood might suffice and that transfusion was a supplement to such measures in extreme hemorrhage as compressive bandaging of the lower extremities, elevation of the legs and the exhibition of digitalis and various drugs then considered stimulants.[3]

[3] *Medical Rec.* (N.Y.) **9:** *Passim,* 1874. An army surgeon, B. E. Fryer, "Transfusion of blood with a modification of the apparatus of Aveling," *Medical Rec.* (N.Y.) **9:** 201–203, 1874, recommended decoagulation with "3 or 4 drops of ammonia solution." In default of blood to transfuse in severe hemorrhage,



HOWE'S APPARATUS.

HOWE'S APPARATUS

In 1874, J. W. Howe, of New York, reported a successful transfusion of undefibrinated blood using Dieulafoy's aspirator, essentially a closed circuit aspirating pump, which he placed in a basin of warm water during the operation. He objected to the use of defibrinated blood since he thought exposure to the atmosphere deleterious—especially in hospital—and that removal of the red globules by defibrination was harmful: "the nutritive and stimulating properties of the blood depend mainly on the presence of these globules." He suspected that the time spent in defibrinating the blood might sometimes delay transfusion too long for it to be effective, and "the wounds in the veins being comparatively large, there is more or less danger of phlebitis or thrombosis" (14).

he recommended this solution:

Sodium chloride	60 grains	(3.840 Gm.±)
Potassium chloride	6 grains	(0.384 Gm.±)
Sodium phosphate	3 grains	(0.192 Gm.±)
Sodium carbonate	20 grains	(1.280 Gm.±)
Water	20 ounces	(840 ml.±)

The aspirator was placed in a basin of warm (100°–110°F., 38°–43°C.) water, and blood was drawn from the donor's vein into a glass cylinder where it was sometimes mixed with a solution of ammonium carbonate as an anticoagulant, but sometimes injected without modification. It was almost immediately pumped into the recipient's vein. A tourniquet was applied to the donor's arm, aspirator stopcocks *h* and *g* were closed, the piston was raised and held in place by a spring. The hollow needles, *f*, measured three inches (7.5 cm. ±) by 2.5 mm. and were connected by gum rubber tubes about five inches (12.5 cm. ±) long, *b*, to stopcock *h* and introduced into the donor's median basilic vein from above downward. The recipient's vein was entered by canulation only when percutaneous venipuncture was

unsuccessful. Stopcock *h* was opened and the blood flowed into cylinder *a*, which might or might not contain an anticoagulant solution, but which did contain a small degree of negative pressure. Frequent digital compression of rubber tube *b* kept the donor's vein from collapsing. A canula and trocar, *c* or *d*, was introduced into the recipient's vein, and the trocar left in the cannula until the actual transfusion was to begin. Tube *e*, of slightly larger calibre than *b*, attached to stopcock *g*, was filled with blood to evacuate the air by gentle turning of the aspirator handle. When the trocar was withdrawn, tube *e* was attached, and the blood was slowly injected.

II

In a lecture given at Pennsylvania Hospital early in 1877, Morton provided a brief introduction to the clinical use of blood transfusion in non-obstetrical practice, mentioning that in 1795—"or thereabouts"—Dr. Philip Syng Physick transfused in a case of postpartum hemorrhage, concluding that "this was undoubtedly the first time the operation was performed in America." He mentioned that Dr. George McClellan, of Philadelphia, reported transfusion in a patient suffering from cholera in 1832, but gave neither details nor bibliography. Morton knew of Blundell's work and gives some attention to an analysis of his reports (15).

When Morton began his work with blood transfusion, he was not using an untried method but he attempted to apply a technique successfully used in a few cases to the needs of general surgical practice. He noted, "An examination of the records of transfusion shows that the operation has been more frequently and successfully performed in cases where death has been imminent from simple loss of blood" (15). In his 1877 lecture, Morton reported that over 56% of 103 patients recovered when transfused after "pure post partum hemorrhage" and over 58% of 41 patients transfused after wounds and operations recovered. Morton himself felt that transfusion was applicable in hemorrhagic diatheses as well:

"We find in hemorrhages generally—not only traumatic, post-partum, or from the intestinal tract, but in those peculiar dyscrasias or blood changes in which we recognize the hemorrhagic diathesis, or a predisposition to purpura hemorrhagica—the operation of transfusion has given the best results. There are many instances, of course, of alarming hemorrhage

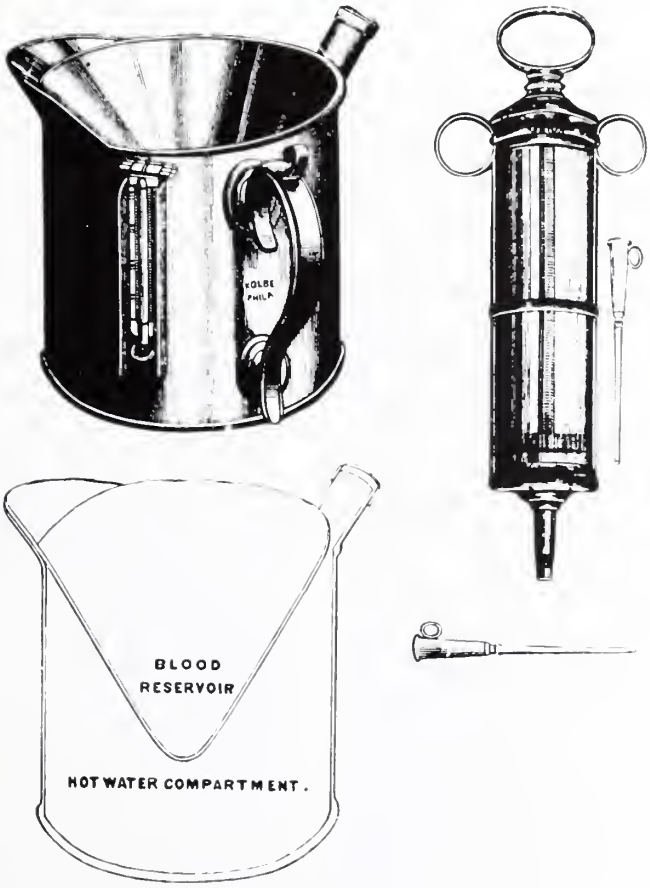
Thomas G. Morton's Cases of Mediate Transfusion with Defibrinated Blood

Case	Year	Quantity ml. ±	Clinical Diagnosis	Outcome	Transfusion Reaction	Survival
I 27WM	1869	330	Hemorrhagic diathesis; lacerated wound of face and jaw	Temporary improvement; death	Moderate	20 days
II 45WM	1870	220+	Carcinoma of stomach	Improvement; death	None	4 months
III 14WF	1874	a) 60 b) 180	Purpura; alveolar hemorrhage after tooth extraction	Recovery	None	Living and well
IV 45WM	1876	120	Compound comminuted fracture of femur	No change; death	None	21½ hours
V 36WF	1876	90	Uterine tumor; resection; postoperative hemorrhage	Recovery	Severe	Living
VI 26WM	1876	105	Anemia, probably pernicious	No change; death	None	1¼ hours
VII 15WM	1877	540	Amputation of leg; postoperative hemorrhage	No change; death	None	3 hours
VIII 35WM	1878	240	Amputation at shoulder joint; postoperative hemorrhage.	Moribund when begun; death.	None	1 hour
IX 30WM	1878	150	Suicide by opium poisoning	No change; death	None	3¼ hours

which are controlled by the well-recognized hemostatics, and it is a matter of surprise how soon after immense loss of blood some patients react, and appear to make up what has been lost; but occasionally a sudden outpouring of blood shocks the nerve centres so profoundly that reaction will not occur, and death and the cessation of the hemorrhage are not unfrequently simultaneous; while again there are cases where, after the hemorrhage has been controlled, the shock from the loss of blood is so great that stimulants lose their power, and reaction is uncertain. In these cases transfusion of blood promises to save life, and should always be resorted to. The same may be said of loss of blood occurring in the hemorrhagic diathesis, and of those cases of bleeding from the intestinal tract which occasionally present themselves in the course of typhoid and other fevers." (15).

Morton outlined definite indications for and contraindications to blood transfusion: he did not recommend its use in phthisis, and advised against it in carcinoma, thereby differing from the opinion of continental workers. He cited Dr. McClellan's 1832 transfusion in a patient with cholera, and while this particular patient died, Morton stated that in similar circumstances, he would have transfused. He considered transfusion "useful" for scurvy, but valueless in pyaemia, septicemia, puerperal fever, tetanus, epilepsy and the exanthemata of childhood (15).

In 1874, Morton reported three cases of transfusion, the earliest in 1869 (16). He used defibrinated blood, and felt that there was little



Morton's Apparatus

danger from introduction of clots and air. He believed that the use of defibrinated blood offered certain advantages: the donor's blood, "venous when drawn, is partially oxygenized by its exposure during defibrination," the amount injected could readily be measured, haste was avoided and the blood was both drawn and defibrinated away from the patient. These early transfusions were performed with a five by one inch (12 x 2.5 cm. ±) glass syringe, metal bound, with hard rubber at each end, holding two ounces (60 ml. ±). A tapering hard rubber nozzle one and a half inch (3.75 cm. ±) long fitted into blunt steel cannulae measuring two by one-twentieth inches (5 x 0.2 cm. ±). Fibrin was removed by agitating the blood with whisks made of broom straw about one by six inches (15 x 2.5 cm. ±) and subsequently straining it through fine linen (17).

His 1874 cases are as follows:

Case I. *Lacerated wound of face and jaw; hemorrhagic diathesis; continued hemorrhage; ligation of the common carotid artery; transfusion; death from rupture of the jugular vein.*

W. P., 27 year old white man, was admitted to Pennsylvania Hospital 15 October 1869 because of continuing hemorrhage from a laceration of the upper lip and jaw sustained when he fell on broken crockery eight days earlier. Excessively weak on admission from loss of blood, his mouth was full of clots. Plugs of lint saturated with persulphate of iron proved ineffectual and hemorrhage could be controlled only by pressure to each side of the nose. Hemorrhage recurred, and was controlled by a long acupressure pin passed through the upper lip and secured with a silk ligature until 19 October, when further bleeding necessitated compression of both facial arteries by acupressure pins passed through the lower jaw, but without success. Ligation of the external carotid artery was impractical, and since the patient was nearly exsanguinated and already unconscious, the common carotid artery was tied, but slight oozing continued.

The following day, the patient was comatose and seemed to be dying. At 4 P.M., eleven ounces (330 ml. ±) of defibrinated blood obtained from two medical students were given. A marked rigor followed transfusion, but two hours later, the patient was semi-conscious. The next day he was able to sit up, perfectly rational, and had no further hemorrhage. "He continued to improve till November 3d, when the internal jugular vein gave way, causing death on the 5th of the same month. The operation of transfusion prolonged the life of the patient over two weeks."

Case II. *Suspected carcinoma of the stomach; marked leucocythemic symptoms with great prostration; transfusion; relief; death four months afterwards from cancer.*

In August, 1870, C. K., 45 year old white man suffered from gastric symptoms with jaundice and dysentery, much anorexia and weight loss, and many episodes of vomiting often mixed with blood. "He had been a very free liver; used to late suppers, and had for years drank to excess." No abdominal tenderness or tumor. The patient improved somewhat on a milk diet, but by late September, was confined to bed. There was some edema of the hands and feet, the skin, mucosa and gums were "absolutely blanched." Death seemed inevitable and in November, transfusion was suggested, "for should the disease be cancer, life would likely be prolonged, and if his disease should prove simply an inability of the digestive organs to assimilate, a favourable change might be induced by transfusion."

On 12 November 1870, rather more than six ounces (200 ml. +) of defibrinated blood were injected into the left median basilic vein without unpleasant symptoms, and the following day there was a marked change for the better. Two months later he began to fail and he died 23 March 1871. At autopsy, there was an ulcerated carcinoma of the upper surface of the stomach. "In this case the transfusion gave temporarily a new lease of life; for the patient could not have

long survived the terribly prostrated condition he was in at the time of the operation."

Case III. *Haemorrhoea petechialis; repeated epistaxis, associated with alveolar hemorrhage; almost fatal prostration; transfusion twice performed at intervals of six weeks, with recovery.*

I. H., an eleven year old white girl was in apparently good health until September, 1871, when sudden copious bleeding from the left nostril and bladder began. There were many petechiae and ecchymoses, and she was confined to bed with some bleeding almost every day for nine months. In September, 1872, severe hemorrhages were nearly fatal, her body was again covered with petechiae with enormous extravasations of blood on front of the legs. On 2 February 1874, a third attack: "the child was drenched with blood and exceedingly prostrated." Alum water and nasal packs controlled the flow. On 8 February, hemorrhage recurred: the child was nearly exsanguinated with hematemesis, no palpable radial pulse, cold extremities and apparently death was imminent.

After much difficulty the median cephalic vein was opened and two ounces (60 ml. ±) of defibrinated blood were given: the pulse was again palpable and the child had a quiet night. Slight bleeding from the nose stopped by itself and on 13 February, the child was up and about, continuing well until the afternoon of 29 March 1874, when hemorrhage occurred from the site of a tooth which had fallen out. By evening, ecchymotic patches and purpura with severe nasal hemorrhage had developed. When seen at 11 P.M., the patient was almost bloodless; bathed in cold sweat, without palpable pulse and obviously dying. Six ounces (180 ml. ±) of defibrinated blood were soon given into the right saphenous vein with good effect. Up and about by 7 April, she was in perfect health by 26 May.

"The rapid improvement and recovery following each transfusion, presents a marked contrast with the tardy convalescence, with confinement to bed during nine months, which followed the first hemorrhage in 1871; while the transfusion, which was performed twice in this patient, is rendered more interesting from the fact of the subject being so young."

In this 1874 report of transfusion in three cases of his own, Morton refers to four other cases not performed by him but which are reported in insufficient detail for evaluation. These suggest that blood transfusion was under active investigation in Philadelphia, and may have contributed to Morton's own more careful and detailed studies.

Case A. A woman suffering from "hydraemia consequent upon long-continued and repeated uterine hemorrhages in connection with a stubborn though mild type of intermittent malarial fever" was given at least six ounces (180 ml. ±) of defibrinated blood by Dr. William Carroll, and soon rallied. Pregnant eighteen months later, she "had ceased to employ Dr. Carroll and fell into the hands of a very unskilful practitioner." She died from postabortal hemorrhage.

Case B. A 26 year old physician with purpura hemorrhagica, tuberculosis, cervical adenitis and frequent nosebleeds bled from his posterior nares, then his gums, then from his oral mucosa: seven or eight ounces (210–240 ml. ±) of defibrinated blood were given. Six or eight hours later the oozing blood began to coagulate, then stop. The patient survived a month.

Case C. A man who fell under a railroad car 3 July 1869 while drunk had his leg crushed, and was admitted to Pennsylvania Hospital under the care of Drs. Agnew and Hewson. He was transfused while in shock, and improved somewhat. His leg was amputated ten or twelve hours after transfusion, but he died 19 July.

Case D. During the summer of 1869, a patient was seen by Dr. Gross because of hemorrhage from the bowels. The patient's veins were collapsed, transfusion was diffi-

cult and unsuccessful, the patient dying shortly thereafter.

In his 1877 Pennsylvania Hospital lecture, Morton mentioned four additional cases of transfusion:

Case E. In 1875, a fifty year old man was seen with Dr. William Pepper. The patient had rapidly become ill, and he was moribund two months from the onset of symptoms. On 30 April 1875, an unspecified amount of blood was given with slight subjective improvement and on 6 May 1875, 5½ ounces (165 ml. ±) of defibrinated blood were given. Later in the day, there was a rise in temperature, the patient was livid and restless. He complained of a headache, became unconscious nine hours later and died fifteen hours after transfusion.

Case F. A seven year old boy suffering from severe epistaxis and purpura hemorrhagica was transfused, but no further details are given.

Case G. A two and a half ounce (75 ml. ±) transfusion was given a patient at the Jewish Hospital suffering from severe anemia, but the patient died two hours later.

Case H. Very early in the 1870's, a nineteen year old boy with a gunshot wound of the femur was transfused, but died ten hours later. No further details are provided.

III

Dr. Morton was a careful and conscientious operator who was thoughtful enough and adventurous enough to increase the surgical armamentarium of his time. He knew of British animal and clinical trials of transfusion, had himself used transfusion a number of times, and was aware of both the risks and possible benefits of this procedure. Sometime between 1870 and 1876, since he does not cite when the experiments were performed which he reported in January, 1877, he undertook his own animal experiments. Modern readers might cavil at a lack of controls and the statistical insignificance of his numbers, but his work deserves reviewing: he began with the problem of accidental injection of clotted blood.

. . . In a medium-sized mongrel bitch that had been etherized, I opened the femoral vein in the left leg, and drew out about two ounces of blood [60 ml. ±] into a warmed receiver; when this had been exposed about twelve minutes, and clot had formed, it was beaten so as to break up the clot, and one ounce was injected into the femoral vein of the other leg . . . the next day the animal seemed rather stupid, but took food, and in three or four days seemed as well as ever. . . . She continued in this good condition for a week, when she was killed by means of chloroform. Dr. Morris Longstreth, pathologist to the Pennsylvania Hospital, has kindly furnished the following report of the post-mortem examination: "Nothing abnormal was found anywhere in the body except in the lungs. . . . The lateral and posterior portions of both lungs about equally presented whitish raised spots, varying in size from a large pea to a grain of wheat. There color was not pure white, but merely whiter than surrounding lung; they were not projecting or pedicellated portions, but merely made prominent by the partial collapse of surrounding lung. Some few of these whitish places now showed very small red, almost hemorrhagic centres on the pleural surface. There also now came prominently into sight much more numerous patches having a hemorrhagic appearance. Their size was in general about that of a grain of wheat. These hemorrhagic-looking points were not surrounded by any white area; they had not increased resistance, as determined by pressure of the fingers. On section of the whole lung the appearances just described were found mostly limited to the surface of the organ. The section of an individual white nodule showed its figure to be nearly spheroidal. In no instance did the figure appear wedge-shaped. . . .

"The larger vessels of the lung contained no clot. The cavities of the heart contained

no fibrous clots. The vein of hind leg was apparently obliterated at the seat of operation; above this point the vessel as well as the ascending vena cava were normal. . . ."

It is plain that exactly what was expected had here occurred. The clots thrown in had gone from the heart to the lungs, and been there as it were filtered out, and the question now arose whether these small pieces would excite abscess or be themselves absorbed.

To determine this, another dog that had been injected with one ounce of blood, which blood had been exposed for over fifteen minutes, and was so full of clots that the canula was once or twice choked by them during the operation, was killed at the end of two weeks. Dr. Longstreth says: "Nothing abnormal was found except in the lungs. On removal of the lungs their surface presented whitish spots having irregular figures, and varying in size very greatly, none larger than a two-cent piece.[4] Those spots never became prominent above the surface as in the former case. There were seen no distinctly red areas. On section of the lung, which was crepitant throughout, it was found that the whitish areas were limited to the surface of the lung, extending below the pleural surface very little more than a line[5] or two in depth. As the knife cut through them it seemed to meet with slightly greater resistance, indicating increased firmness at these whitish spots. The immediately adjacent lung showed no hyperaemic zone, and the pleural surface was normal. . . . No clots were found in the heart cavities." It is evident that the lungs were regaining their normal condition, and in this case at least, no bad results would have followed the injection of clot. To make the matter more certain, however, I made one more experiment.

I injected a small and active mongrel dog with one ounce of clotted human blood, which had been exposed for about two and and one half hours. There were some symptoms of constitutional disturbance; but when at the end of three weeks the animal was killed he seemed perfectly well, and Dr. Longstreth reported that nothing abnormal was discovered in the lungs or in any other part of the body.

Now it would not do to say that in a human being, especially in one with a tendency to scrofula, such experiments would be safe; but I have earned the right to declare that the injection of a small amount of clot is not nearly so dangerous as it is supposed to be, and it is to be remembered that under no circumstances would a patient receive as much clot as was injected into the veins of the subjects of these experiments.

Another bugbear, in spite of the experiments of Blundell, is the injection of air, which it has been often said would be instantly fatal. Some years since, at my suggestion, Dr. W. B. Hopkins injected air in a number of dogs without unfavorable results, and I have lately performed the following experiments:

I injected into the femoral vein of a good-sized dog four drams [16 ml. ±] of air; a distinct bubbling noise was heard as the air passed into the vein. The animal was considerably depressed, but mainly, I think, from the prolonged use of ether. He was carried into the open air, and water thrown over him freely, when he was soon able to get on his legs, although very weak. No unpleasant symptoms followed, and a day or two after he seemed in perfect health.

Two drams [8 ml. ±] of air were injected into the femoral vein of another dog. He recovered more rapidly than the first one, and showed no bad effects. (16)

IV

Between 23 December 1876 and 15 November 1878, Morton performed mediate transfusion of defibrinated blood on his surgical service at Pennsylvania Hospital on six occasions. He had made a few empiric trials of this between 1869 and 1875, he was familiar with

[4] The size of a modern five-cent piece, approximately 2.1 cm. in diameter.

[5] A *line* is one-eighth of an inch, approximately 3 mm.

the efforts of other workers, and had done some careful animal experiments to ascertain the possible effects of injection of clots and of air. Perhaps these six transfusions were a concerted clinical trial: this is conjectural, but permanent modern record keeping begins at Pennsylvania Hospital in 1872, and review of the volumes of bound case records immediately before and after these transfusions turns up no cases of transfusion before or after, even in comparable injuries and illnesses occurring on Morton's own service. This confirms a suspicion that Morton was trying the technique on a larger scale than hitherto done.

These six cases are as follows:

Case IV. (P. H. ✱1876–1296) *Compound comminuted fracture of the thigh; great loss of blood; transfusion; death.*

G. W., 45, a policeman, was admitted 23 December 1876 following a compound comminuted fracture of the lower third of the femur while attempting to stop a runaway team at the corner of Race and Vine Streets. The pulse was imperceptible at first, then thready; the tissues around the fracture were described as "boggy." The femoral artery was tied although there was no bleeding from it, whiskey and ammonium carbonate were given subcutaneously with ten minims of Magendie's solution of morphine.[6] Four ounces (120 ml. ±) of defibrinated blood obtained from his 22 year old daughter were given at 12.15 A.M. 24 December in two equal aliquots, each requiring two and three-quarters minutes for administration into the right radial artery. Some pain in the wrist and hand was noted during the transfusion. "There was no rigor, no shudder, and no apparent embarrassment of respiration." Although there was no objective change in the patient's condition, he said that he could "see better." He died twenty-one and a half hours after the transfusion.

Case V. (P. H. ✱1876–1282) *Vascular tumor of vagina; great loss of blood; removal of the growth; profuse bleeding; exhaustion; transfusion; recovery.*

E. P., 36, a housewife, was admitted 27 December 1876 because of five months of vaginal bleeding. Six days before admission there was a sudden hemorrhage, and the patient stated that "a gallon" of blood was lost. She was a pale, anemic woman with a vaginal tumor two inches in diameter, irregular and moderately hard with a fetid, scanty, purulent discharge. "After etherization, the growth was found to be attached to the vagina, mainly upon its posterior aspect, and also slightly to the posterior lip of the uterus." This was removed with "considerable" loss of blood, and alarming postoperative prostration. Pulse weak and irregular, the patient vomiting and unable to retain even champagne. At 5 P.M. 27 December 1876, three ounces (90 ml. ±) of defibrinated blood from her eighteen year old daughter were injected into the left antecubital vein. Ten minutes later, the pulse was fuller at 140 to the minute, but at 5.30 P.M., she was "seized with a violent series of rigors; vomited; gasped for breath," and was treated by external warmth and the application of mustard to the abdomen, chest and legs. She was given enemata of brandy and beef tea, a small dose of ammonium carbonate by mouth and a quarter grain (16 mgm.) of morphine by skin. She was discharged improved—but still with "considerable disease of vagina"—on 28 February 1876.

Case VI. (P. H. ✱1876–1254) *Profound anemia; transfusion; death.*

J. F., a 26 year old man, was admitted to the service of Dr. J. M. DaCosta on 14 December 1876. Unwell and generally debilitated since the previous summer, there was a history of "jaundice" dating to two and a half years before admission. Stools were slate colored, urine scanty and dark with ankle edema. Headaches had been severe enough to interfere with sleep, and he complained of feeling "boozy." He had

[6] Ten minims is about 0.6 ml. Magendie's solution of morphine contained 61 grains to the ounce, about 14% w/v.

always been subject to nose bleeds, and at age twenty had had a chancre. On admission, temperature 103°F. (39°C.). Skin light yellow but sclerae pearly white. Urine amber, specific gravity 1.012, no sugar, albumin or bile. No splenomegaly or lymphadenopathy. Liver dullness extended to the costal margin. Soft apical systolic murmur and dullness to percussion noted at the apex of the left lung.

He felt better after exhibition of dilute phosphoric acid, twenty drops, and elixir of iron pyrophosphates, forty drops, four times daily, but his tongue continued to be dry, coated and cracked. Fingernails were described as lacking smoothness and gloss. On 4 January 1877, extreme deficiency of the red corpuscles was noted without increase in the number of the white. A few days later, the grasp in the patient's hands was described as weak, and ophthalmoscopic examination revealed pallor of the discs. Neck veins were full and there was throbbing of the carotids.

On 10 January 1877 following severe nose-bleeds, the patient was restless and delirious with a feeble pulse. Three and a half ounces (105 ml. ±) of defibrinated blood was given into the left radial artery over seven and a half minutes. He died one and one-quarter hours after transfusion. "At the autopsy, five and one-half hours after death, the blood was found more fluid than usual, indeed it was actually watery: but neither gross nor microscopical examination of the bones, lungs, heart, liver, spleen, supra-renal capsules, nor kidneys showed anything to account for death, and it cannot be said that the cause of his disease was discovered."

Case VII. (P. H. ⅋ 1877–1675) *Crush of leg; amputation at knee joint; secondary hemorrhage; translation; death.*

C. S., 15 year old schoolboy, was admitted 31 March 1877 following a severe crush injury of the left leg, and amputation at the knee joint was performed. Some bleeding was noted on 5 April, and at 10.30 P.M. 7 April, seven days after operation, there was massive hemorrhage—about sixteen ounces (550 ml. ±)—from the amputation stump with great shock. The stump was opened and the tissues seemed to be sloughing. A tourniquet was applied and at noon 8 April 1877, three ounces (90 ml. ±) of defibrinated blood were injected into the left antecubital vein. No change was noted either way, and the patient died three hours after transfusion.

Case VIII. (P. H. ⅋ 1878–267) *Compound crush of arm; amputation at shoulder joint; secondary hemorrhage; transfusion; death.*

R. McD., 35 year old factory hand, was admitted 17 May 1878 because of a bad crush of the right arm for which amputation at the shoulder joint was performed. There was moderate postoperative slough of the stump, but he did fairly well until 25 May, when, at 3.30 A.M., there was a violent hemorrhage. Respirations were six to the minute, no radial pulse was palpable, the extremities were cold and there was no response to hypodermic injection of 30 minims (1.5 ml. ±) of whiskey and one and a half grains of ammonium carbonate (90 mgm. ±). Eight ounces (240 ml. ±) of blood "obtained from a healthy patient who gave it without asking, rather a rare thing in hospital experience" was injected into the median cephalic vein. The blood not moving freely, the canula was removed and some additional blood was injected into the left femoral vein. The operation itself occupied about two minutes, during which time artificial respiration was kept up, but death occurred at 4.30 A.M. Autopsy revealed that the axillary artery had sloughed one inch (2.5 cm. ±) above the ligature.

Case IX. (P. H. ⅋ 1878–1055) *Opium-poisoning; transfusion; death.*

J. G., 30 years old, male, was admitted to hospital at 10.10 A.M. 15 November 1878, unconscious. Respirations were stertorous, between three and six to the minute. Throat and nostrils were filled with mucus, heart feeble and pupils pinpoint. He was said by

neighbors to have taken laudanum during the previous night, and was not discovered until nine A.M. Shortly after admission, a well-marked opium fit occurred which lasted one half to one minute, and during which time respirations were suspended. An attemp to pass a stomach tube was unsuccessful. Twenty grains (1.2 Gm. ±) of zinc sulphate emetic were given and repeated three times without effect. An hour later, the stomach was successfully washed out. The gastric contents were very black, and smelled strongly of laudanum. Hot coffee was injected into the stomach, and one-tenth of a grain (6 mgm.) of atropine was given subcutaneously.

By 2 P.M., the pupils were dilated, but artificial respiration could be discontinued for a time, with spontaneous respirations at eleven to the minute. He was given hypodermic whiskey, digitalis and ammonium carbonate. Two drops of croton oil on the tongue and a turpentine enema were without effect. Stimulation with Faradic electricity was ineffectual.

The patient was bled sixteen ounces (480 ml. ±) from the temporal artery and left arm which, with the application of cold to the chest and artificial respiration had restored respirations. At six P.M., the pulse was weak at 130, and the heart action very feeble with slow respirations. Five ounces (150 ml. ±) of defibrinated blood were given into the long saphenous vein. Respirations increased and the patient was again able to breathe without assistance. He rallied, and by eight P.M., respirations were twelve to the minute. At 9.15 P.M., he was breathing fifteen to eighteen times to the minute, but died shortly after this.

V

Although there had been sporadic attempts at blood transfusion all through the nineteenth century, and before, sustained experimental and clinical trials of blood transfusion were conducted by Blundell and Aveling. Their work is well known—Morton's is not. Isolated instances of transfusion are interesting and instructive examples which may provide a basis for other men's work, but nineteenth century physicians demanded more rigorous proof of the efficacy and safety of a procedure than can be provided by a single case report. This proof Morton undertook: we do not know why he abandoned the technique, but abandon it he did.

Of his nine cases, two (III and V) were very close to death from exsanguination and recovered, one (V) despite a severe transfusion reaction. One case (II) improved subjectively, and died of carcinoma four months later. One hemophiliac (I) seems to have been helped over his immediate problem, but died of further hemorrhage. One (VIII) was to all intents and purposes dead when transfusion was begun. One case of suicidal opium poisoning (IX) died after nearly a full day's heroic supportive therapy and after what must certainly have been an attempt at exchange transfusion. Three cases (IV, VI and VII) were failures. Thus, eliminating the case dead when transfusion was given (VIII), of the remaining eight, four (I, II, III and V) were clinical successes, and four (IV, VI, VII and IX) were clinical failures. Again omitting the case dead when transfusion was begun, one case (I) transfused with blood from two donors at the same time had a moderately severe transfusion reaction, and one (V) had a severe transfusion reaction. The other six cases, including a girl (III) twice transfused with blood from different donors, apparently had no reactions.

Prior to the discovery, in 1901, of the human blood groups, such transfusion reactions would have been a frequent complication of transfusion. Yet, assuming that the distribution of groups ABO in the white population has not changed over the last century, and there is no reason to think that it has, sixty-five out of a hundred individuals transfused at random with blood drawn at random from the same population would have received ABO compatible blood quite by chance.[7] Morton's choice of family members as donors would perhaps have

[7] In the white North American population, blood

increased this enough to offset the risk of transfusion reactions due to incompatibilities other than ABO, which amount to less than one per cent of such reactions. Nor are all transfusion reactions fatal.

It seems doubtful that even in the event of active spirocetemia the pale treponeme would have survived Morton's defibrination technique, so that spread of syphilis by transfusion would not have been a problem. Bacterial contamination might have occurred through manipulation, but in an otherwise healthy individual suffering surgical trauma, this need not have been an overwhelming problem. Infectious hepatitis would have been neither less nor more of a risk then than now—less certainly than that involved in the use of pooled plasma.

Morton preferred to defibrinate blood to prevent clotting by beating it with straw whisks in the blood-warmer which he prepared. He felt that there was little difference in the red cell content of the blood before and after such treatment, but lacked quantitative proof of this: as it turned out, he was right.[8]

His experimental and clinical trials of transfusion were abandoned. In retrospect, apart from the problem of transfusion reactions, many of his clinical failures seem to have been due to "too little, too late," yet his attempt reflected thoughtful experimental design and careful clinical investigation of too high an order to merit oblivion. His advice, "Only be reasonably careful of clot and air, and especially avoid throwing in the blood rapidly. It can hardly be thrown in too slowly"[9] remains valid and can be profitably recalled today.

groups in the ABO series occur as follows:

Group O	45% of both donors *and* recipients
A	41%
B	10%
AB	4%

In 100 random unmatched transfusions, 45 group O individuals could safely receive only group O blood, therefore, 20 (45% of 45) would receive compatible blood, and 25 (55% of 45) would not. 41 individuals with group A blood could receive group O (45% of 41 = 18) or group A (41% of 41 = 17) so that 35 would get compatible blood and 6 would not. 10 group B individuals could receive group O (45% of 10 = 5) or group B (10% of 10 = 1) so that 6 would get compatible blood and 4 would not. Finally, the four fortunate group AB individuals would find group A, B, O or AB blood compatible.

[8] Using whisks prepared from an ordinary broom and Dr. Morton's blood warmer, which has survived in the Pennsylvania Hospital, two ounces (60 ml. ±) of blood were defibrinated following Morton's directions. The process was conducted at the recommended temperature and was complete in three and a half minutes, the majority of the "fibrin" coming off at two minutes, and very little thereafter. Studies performed on 3 May 1961, in the pathology department Dr. Morton once headed, gave the following data:

	Before Defibrination	*After Defibrination*
Hemoglobin	16.1 gm.%	17.1 gm.%
Hematocrit	49%	51%
Red cell count	6,300,000 c.mm.	6,200,000 c.mm.

The writer is obligated to Mr. Richard Brady for volunteering his blood, unusual in hospital practice and perhaps unprecedented in medical historiography, and to Miss Patricia Distel for performing the blood counts.

[9] See reference 15.

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A Note on the Morton Dressing Carriage

By JOHN B. BLAKE, PH.D.[1]

DR. JOHN H. NODINE has recently described a very interesting model of an antique dressing cart made in 1869 by Mr. James Godfrey, son of the chief maintenance man in the machine shop at the Kirkbride Infirmary (1). It is of some interest, therefore, to know that the original design of the actual cart which this model follows was the work of Dr. Thomas George Morton (1835–1903), the Philadelphia surgeon, who introduced the carriage into the Pennsylvania Hospital in August, 1866. It proved to be an immediate success. Quickly adopted by other hospitals in Philadelphia, it was commended even abroad, and ordered for a number of European hospitals (2). In 1876 it received a certificate of award from the United States Centennial Commission (3). It was still being used, in a modified form, as late as the 1890's, (4) although simpler carts, easier to clean, were replacing it in the best practice (5).

The idea of a ward dressing cart seems so elementary now that it is difficult to imagine what conditions were on the surgical wards of the Pennsylvania Hospital before its introduction. In most hospitals of 1866, according to Morton, there were a number of sponges and tin or earthenware basins for washing wounds—generally one basin and one sponge for each patient—which after use were placed still damp under the patient's bed to dry, until they were used again on the next round. The inevitable result was contaminated air and odorous sponges and basins. Morton found the common technique of sponging and re-sponging wounds from the same basin equally objectionable, on the grounds that only flowing water should be used, so that water which had once been in contact with the wound would not touch it again.

[1] Curator, Division of Medical Sciences, Smithsonian Institution, United States National Museum, Washington 25, D.C.

Morton's dressing carriage did away with the basins and sponges and provided a fresh supply of running water for each wound. In its first form (fig. 1) it consisted of a table about three feet high, three feet long, and seventeen inches broad. The rims of the three wheels were covered with leather, the smaller one in front being on a pivot. On top in the center was a reservoir holding six to eight gallons of water; to this was attached a ten-foot rubber tube with a nozzle at the end and appropriate stopcocks. On either side were places for bandages, lint, adhesive plaster, and jars for holding lint soaked in various solutions. Drawers in each end held towels and instruments. A large tin bucket with a projecting lip taking up half the space under the table received all the refuse dressings, water, and oakum—the last being used instead of sponges, which were too expensive to use only once, but exceedingly difficult to clean. The second can contained two compartments, one for fresh oakum, cotton, and linen, the other for soiled bandages. A can for hot water, to heat the adhesive plaster, completed the apparatus (6).

During the next couple of years, several improvements were made in the carriage, including sturdier construction, accurate partitions on the top for the various bottles (which actually made it harder to clean and were later eliminated), a rack to hold the wardbook, and a copper can for hot water, with an alcohol lamp, carried in ring brackets at the front end, conveniently below a covered, grooved space for adhesive plaster (fig. 2) (2). The model made by Mr. Godfrey has these improvements.

The most vivid description of the benefits that accrued from Morton's apparatus, and an illuminating glimpse into the details of hospital management a century ago, comes from the pen of Dr. William Hunt:

> The contrast at dressing hours [he wrote], before and since its introduction, is very

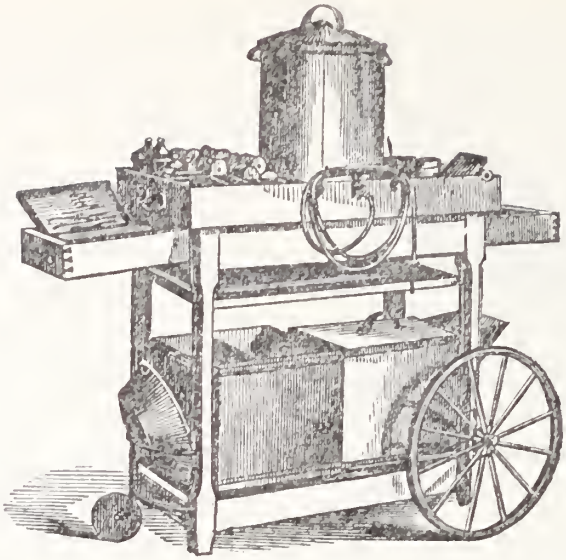

Fig. 1. Original Morton dressing carriage (Courtesy of National Library of Medicine).

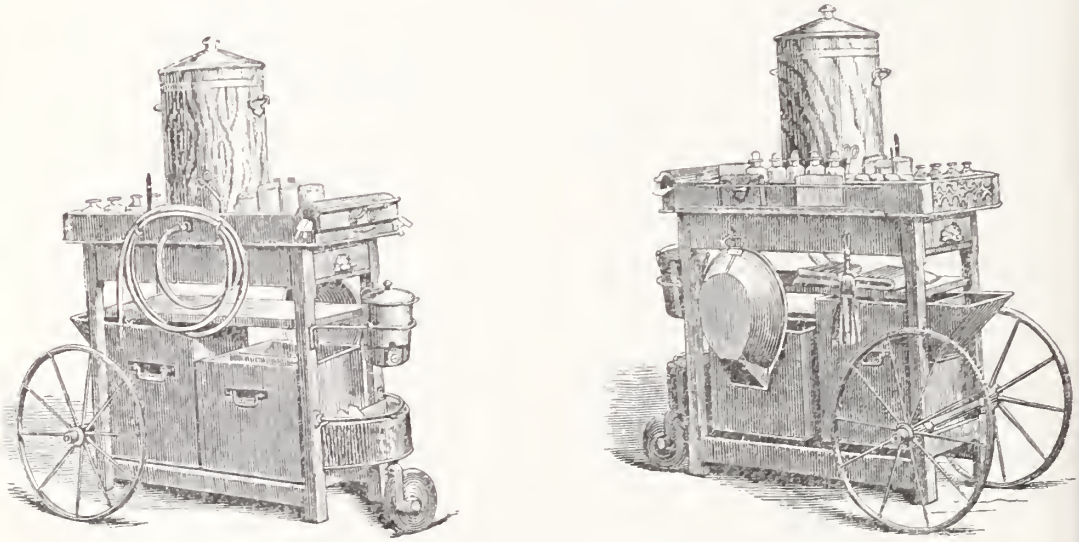

Fig. 2. Improved dressing carriage (Courtesy of Smithsonian Institution).

marked. Then, the head nurse, with his regular assistant, and one or two limping and clumsy convalescents, followed the doctor with hand-trays, water-cans, and slop-buckets, taking up and setting down at each bed, and, unless well drilled, awkwardly moving about and stumbling over the impediments, and not unfrequently upsetting them. Now the hands of all are free, and not so many of them are necessary; if anything is wanted the nurse hands it from the carriage, or the surgeon takes it at the required moment; one case is finished, and the little vehicle moves noiselessly on to the next, leaving the new and the clean behind it, and carrying away the old and the soiled.

Then, we remember it was considered something to be proud of in telling, that

every man had his own basins, sponges, and other appliances, kept separately, about and under his own bed, for his own exclusive use. Now such things are discarded, and cumber the floors no more (2).

The convenience of wheeling about the various medicaments, bandages, and instruments required had evidently impressed itself on others before Morton, since we find a description of a dressing cart used in Parisian hospitals in 1862—where, incidentally, a cart was also used to distribute food. In this case, however, the top of the dressing cart covered a compartment for bandages and medicaments, precluding its use as a shelf. The French cart, moreover, did not provide a supply of running water or a convenient means of removing used dressings (7). Further testimony to the originality and value of Morton's invention comes from no less a witness than the English surgeon, T. Spencer Wells, who described the cart and Morton's technique in the *British Medical Journal*, following a visit to the Pennsylvania Hospital in 1867:

> I have not seen anything so convenient, and saving so much labour [he concluded], in any of our own or the continental hospitals; but I am anxious to direct particular attention to this apparatus for the far more important purpose it serves in getting rid of sponges, basins, and a mode of dressing which must tend to render the air of surgical wards impure, and to convey the organic poisons of pyæmia, erysipelas, or other contagious diseases, from one patient to another (8).

After some years' experience, Dr. Morton concluded that the cart had been instrumental in reducing the incidence of pyemia on the wards of the Pennsylvania Hospital, and eliminating it altogether from 1874 to 1879 (9). This was evidence of its usefulness in which he could take justifiable pride.

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Memoir of William Hewson (1877-1960)*

By AUSTIN T. SMITH, M.D.

WILLIAM HEWSON, a Fellow of our College for thirty-six years, was sixth in direct line from father to son in the profession of medicine in Philadelphia. He was the son of Doctor Addinell Hewson, and the great grandson of Doctor Thomas Tickel Hewson, a former President of the College of Physicians. To this remarkable family background he added fifty years of active practice as a clinician; highly regarded and admired by his colleagues for his professional ability and forthright character, and loved by his patients for his devoted concern for their welfare. The first thirteen years of his professional career were spent in general practice, the remainder in the special field of Otolaryngology. He was truly a dedicated physician by both family precept and by deed.

William Hewson graduated from the University of Pennsylvania in 1906 and from the medical school of that institution in 1910. He took his internship at the Pennsylvania Hospital, Eighth and Spruce Streets, and started in general practice in 1912. To him medicine was a way of life, and although his chief interest was clinical practice, he realized the important part academic medicine plays in maintaining proficiency in the changing field of clinical medicine. Consequently, throughout his career he was a teacher in some capacity. He taught embryology at Temple University School of Medicine, and helped to organize the first heart station at the Philadelphia General Hospital. He also took an active part in undergraduate teaching in the department of Otolaryngology at the University of Pennsylvania and rose to the rank of Assistant Professor of Otolaryngology. He was a cooperative and willing worker in this department. He worked well with the students and was considered by them to be a good teacher as well as a good clinician; a fine combination for undergraduate medical teaching.

In addition to his active clinical work in office and hospital, and the time given to teaching, he found time to take an active part in Medical Societies, both as an officer in their administration and by regular attendance and active participation in their meetings. This was especially true of his interest in the Philadelphia Societies: The College of Physicians, The Philadelphia County Medical Society, and The Philadelphia Laryngological Society. He could always be counted upon to do his part in supporting them, whatever the task might be. He served as Clerk and Chairman of the Section on Otolaryngology of the College. His membership in national societies included: The American Medical Association, The American Laryngological, Rhinological, and Otological Society, and The American Academy of Ophthalmology and Otolaryngology. He had many hospital affiliations which kept him active in the city and in the suburban areas. He was Chief of Service at the Abington Memorial Hospital, Roxborough Memorial Hospital and the Philadelphia Hospital for Contagious Diseases. He was also on the active staff of The Pennsylvania Hospital, Graduate Hospital, Children's Hospital, Bryn Mawr Hospital, Presbyterian Hospital, and Methodist Hospital.

He served in a military capacity during both World Wars. In World War I he was a Lieutenant in the Medical Corps of the Navy, on active duty with the Methodist Hospital Unit, Navy Base Hospital No 5, stationed in Brest, France from September 1917 to January 1919. In World War II he was a Lieutenant Colonel

* Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

in the Pennsylvania National Guard and formed the Medical Unit for the First Regiment.

Doctor William Hewson was a cheerful, happy person who found real joy and satisfaction in his contact with patients and colleagues. He had a kindly, gentle manner, but took a firm stand for what he thought was right and proper, and he was not hesitant in vehemently taking such a stand if the occasion demanded it. He was a cheerful, bouyant companion to his colleagues and friends, and they will greatly miss their pleasant associations with him.

Memoir of Charles Camblos Norris (1876-1961)*

By CARL BACHMAN, M.D.

CHARLES CAMBLOS NORRIS was born June 1, 1876 in Philadelphia, and died at his home in nearby Bryn Mawr on February 26th, 1961 in his 85th year.

A member of an old and illustrious Philadelphia family, he attended Episcopal Academy and the University of Pennsylvania, obtaining his degree in medicine from the latter institution in 1898. He then served three consecutive one-year terms as a house officer in, respectively, the Pennsylvania Hospital, the Hospital of the University of Pennsylvania, and the Johns Hopkins Hospital. In 1901, he became associated with John Goodrich Clark as a staff assistant in gynecology at the University of Pennsylvania. In 1927, he became the first member of the University's medical faculty to hold a joint professorship of obstetrics and gynecology. He directed the then newly-combined Department of Obstetrics and Gynecology until his academic retirement in 1941.

Throughout his professional career, Dr. Norris was keenly interested in gynecologic pathology. Shortly following his initial association with John Clark, he organized a departmental laboratory of pathology, which he directed thereafter over a span of nearly forty years. A stream of approximately one hundred published articles, and three books, attest to his special preoccupation with problems of gynecologic cancer, tuberculosis and Neisserian infections. He was one of the early advocates of radiotherapy for uterine malignancy, in an era when the outlook for most women afflicted with such cancer was indeed bleak.

His efforts to extend our knowledge of the diseases of women were recognized by his selection as an advisory editor of the *American Journal of Obstetrics and Gynecology*, the *American Journal of Cancer*, and the *American Journal of Medical Sciences*. His memberships in national professional societies included the American Gynecological Society (President, 1930); the American Gynecological Club; the American College of Surgeons, the American Society for the Control of Cancer (Director, 1929 1936); the American Radium Society; and the American Neisserian Medical Society.

In his professional relationships, Dr. Norris was a self-effacing, good-humored and generous colleague. He was particularly interested in befriending, and enlisting the enthusiasms of, his younger associates. To these he gave freely of his time and counsel. Temperamentally, he neither welcomed nor relished the administrative tasks that his academic accomplishments inevitably imposed upon him; nevertheless, he discharged these duties and missions not only with dispatch, but with practicality and fairness to all concerned. In order that the younger generation should "have the stage" after his retirement, it was characteristic of him that he then divorced himself completely from professional activities.

It was one of his hopes, on retirement, to indulge his life-long hobbies of fishing and small-game hunting. When the restrictions of World War II made this impossible for a time, he set himself the project of writing a book on "Eastern Upland Shooting". Probably to his surprise, and certainly to his gratification, the book was not only accepted for publication, but proved popular enough in this country and Great Britain to require several printings.

Dr. Norris' marriage, rather late in life, to Helen Elizabeth Walshe was a singularly happy one. The home which this sprightly

* Read before the College of Physicians of Philadelphia, 3 October 1961. Prepared by Dr. Bachman and read for him by Dr. Lewis C. Scheffey.

lady graced until her death in 1953 was always open to friends and colleagues, young and old alike, and no more charming hostess and host could any guest desire.

Surviving Dr. Norris are his half-sister, Mrs. Claire Barrow of Savannah, Ga. and his half-brother, Wymberley W. DeRenne of Athens Ga.

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Annual Report of the President, College of Physicians of Philadelphia*

By THOMAS M. DURANT, M.D.

THE Ordinances and By-Laws of our College direct that the President shall, on the occasion of the January meeting each year, deliver an address. Very wisely, I believe, no limitation whatsoever has been placed on him relative to its contents, and I am at liberty therefore to speak as I wish concerning the affairs of our organization. It is my intent to touch briefly on business matters, then to say a few words about the heritage that is ours as members of the College, and, lastly, to discuss our purposes as an organization and what we might do to extend our usefulness to our members, to the medical community, and to the public.

The past year has been a gratifying one from the standpoint of maintenance of financial status despite rising costs and the tremendous expansion of medical literature with which our library must keep pace. In connection with the latter, I am sure Mr. Morse, our fine librarian, must have somewhat the same feeling wise King Solomon expressed, many centuries before the invention of the printing press, when he said, "Of making many books there is no end"†. Even then men must have had a yen for a long bibliography after their names! One of our Fellows, in speaking to me about the literature expansion problem, actually expressed the view that, sooner or later, it is going to be impossible for our library to keep up! I do not share this pessimistic view. It is not going to be easy, but I am sure that it can be done. It *must* be done! I wonder how we Philadelphians would feel if our medical library, so famous not only in the United States but also abroad, were to become a second rate one.

You are familiar with the plans worked out by Dr. Rhoads during his presidency for increasing our endowments. This three-pronged attack included: (1) stimulation of the Fellows to obtain donations from patients and friends, (2) encouragement of each to include the College in his will, through the stimulation of Dr. Scheffey and his committee, and (3) the Weir Mitchell Associate program. There is very satisfying progress along each of these lines, and we owe an especial debt of gratitude to Dr. Blumstein, both for the development of the Weir Mitchell plan and for the great amount of effort he has expended in making it a success. At the present time there are 60 Weir Mitchell Associates. It is to be hoped that before long there will be at least

* Read before the College, 3 January 1962.
† Ecclesiastes **12:** 12.

100. There are still many good journals available for endowment.

There have been many gifts to the College during the year from Fellows, from Charitable organizations, from friends and patients of Fellows. I would like to mention especially a $5,000 gift from Dr. Thorington to the Library Historical Collection, and $25,000 from the Pew Foundation. The latter is to be used for a study of Philadelphia Area Intern and Resident financial needs, and also for the support of our institution. We are indeed grateful for these fine contributions and for all of the others that have helped maintain and advance our Library and the other College activities.

THE PAST

Turning to a consideration of our heritage, it has been a very gratifying and even exciting experience for me this year to become better acquainted with the history of our College and of the great men who have founded it or have maintained it in a position of eminence in the years since its birth. The meeting tonight marks the 175th anniversary of that which took place on January 2, 1787, not long after our country achieved its independence. Dr. John Redman was the first president, and other outstanding charter members were Drs. William Shippen, Jr., Adam Kuhn, Benjamin Duffield, Samuel Powel Griffitts, and Benjamin Rush. There were thirteen founders present at the meeting. A few years later, in 1793, the College was to serve an important function in connection with the terrible yellow fever epidemic that struck Philadelphia in the summer of that year. The aid given by the College to governmental agencies was probably instrumental in leading to the establishment of the first departments of Public Health in this country. It was also out of this epidemic and the polemics that arose in the College meetings that Dr. Rush, a signer of the Declaration of Independence, became additionally famous as well as notorious (in the pejorative sense of that term) because of his massive dose calomel-jalap and multiple venesection therapy. In studying the available details concerning this regimen, however, I am convinced that he could well have achieved some of the dramatic cures claimed by him. In a disease characterized by serious liver damage and bleeding into the gastro-intestinal tract, heroic catharsis certainly could have lessened ammonium intoxication and rescued from hepatic coma. I have no defense to offer, however, for the multiple phlebotomies. A more constructive note from the year 1793 was the publication of the first volume of the College's *Transactions*, to which Rush contributed a paper.

Now moving forward in time to the occasion of the 100th anniversary of the College, January 3, 1887, exactly 75 years ago tonight, we find Philadelphia's famous S. Weir Mitchell officiating as president on the occasion of the Centenary Celebration. Many outstanding physicians were present, but there was one who merits special attention, William Osler, later Sir William. Characteristically we find he was an active member of the Library Committee. The love he developed for the library, which he visited almost daily from 5–6 p.m. during his Philadelphia years, persisted through the remainder of his very active life in Baltimore and in England. While Regius Professor at Oxford many years later he demonstrated that affection by being instrumental in obtaining for us an excellent and priceless copy of a 15th century Celsus which he had discovered in a London book stall. He contributed $25 to its purchase, and asked Weir Mitchell to "phlebotomize the Fellows for the rest." Dr. McDaniel will be happy to show you this fine volume with the letter to Mitchell, signed 'W.O.', on the fly leaf. In addition, Osler remembered this College by a bequest in his will.

THE FUTURE

We do not live in the past, however. We believe, with Shakespeare, that, "What's past is prologue," and, with Thomas Draxe, "The water that is past cannot make the mill go." During the new year and those that follow, it is our duty to increase the contribu-

tion our College makes to Medicine and to Mankind.

How can we do this beyond continuing to improve our library, our collections, and our other present functions? In giving much thought to this I have started with the recognition that we are primarily, and almost solely, an educational institution. Just as the American College of Physicians is an Educational Organization for Internists and related specialists, leaving the socio-economic problems to the Society for Internal Medicine, so the College of Physicians of Philadelphia feels that Education is its major province, the County Medical Society being burdened with a heavy load of socio-economic problems. Differing, however, from the American College of Physicians, the American College of Surgeons and other National Specialty groups, ours is an academy of leading physicians representative of *all of the specialities* in Medicine and of the best in general practice. With rapid medical advance as a centrifugal force tending to drive the specialists farther from each other, from the general practitioner and from the all-important patient, do we not have a unique opportunity to serve as a counteracting centripetal and adhesive force? Dr. Iago Galdston said recently in his excellent paper, *The Birth and Death of Specialties*, "The long view of the history of science reveals the pattern of periodic diversifications in interest and knowledge, that is, of specialization, followed by periods wherein the synthetic unification of knowledge is achieved. Science is never more innately consonant and rewarding than during its unitary stages." Why could we not here in this College work toward the rewarding unity of which he speaks? I am not entirely certain in my own mind how best to approach this problem, but one thought would be the establishment of an Interspecialty Forum for discussion of such problems as headache, low back pain, fluid balance, etc. I pledge myself to work toward specialty cooperation during the coming year, and I sincerely covet your advice and help in this undertaking. I am certain that our College membership contains a cerebral potential so great that good ideas should be plentiful and that the only problem will be to correlate and activate them.

And now I should like to put before you another idea, one which is not my own, but that of a man who previously served as Secretary of the College. Dr. Leandro Tocantins has suggested that the Medical Schools of Philadelphia could enter more fully into the educational activities of the College. A Committee made up of the Deans of the five undergraduate and one graduate medical school in our city could explore the possibilities of greater use of our facilities, of having a neutral forum for the discussion of interacademic affairs, of proving a residency and internship council, and of encouraging more effective and extensive library utilization. I consider this such a potentially profitable scheme that I shall initiate discussions with the Deans and our Council in the hopes that it can be soon activated. Here again I am open to, and solicitous of, suggestions from our Fellows.

And so as we start this New Year I extend greetings and express the hope that each of our Fellows will consider it his responsibility to participate in and contribute to a forward movement of our College in accordance with what would be expected of us by the Weir Mitchells, the William Oslers, and the other great men of our past. Let it not be said of us in the future that we failed to recognize and make the most of the opportunities that are ours in 1962.

The Health Sciences—A Common Bond Among All Nations[1]

By LEROY E. BURNEY, M.D., M.P.H.[2]

THOMAS Henry Huxley stated that, "the great end of life is not knowledge but action." Arthur Parker Hitchens was one of those rare individuals who not only made distinct contributions to scientific knowledge in the golden era of microbiology, but followed through to insure that this knowledge was put to work. He had the intelligence, curiosity, imagination and vision of a great scientist and, in addition, the vigor and persuasiveness to make his ideas become realities.

In his colorful career, Colonel Hitchens served with distinction in the U. S. Public Health Service, Mulford Laboratories, the Army Medical School, as Advisor in Public Health to the Governor General of the Phillippine Islands, and as Professor of Public Health and Preventive Medicine in the University of Pennsylvania. He gave vision and action to the young Society of American Bacteriologists, serving as its president in 1924, and conceived and helped activate the *Journal of Bacteriology*.

Hitchens and his contemporaries really gave birth and impetus to the blossoming field of microbiology in the latter part of the 19th century and the first quarter of the 20th century. There was a very close relationship in training and research between American bacteriologists and European investigators. Early bacteriology owes much, as in other sciences, to our colleagues in other countries. This has continued and become further emphasized in the present era. It is appropriate, therefore, in this Arthur Parker Hitchens Lecture to focus on international health and the urgent remaining needs in the world family of scientists for new knowledge and its application. I am highly honored to have been asked to give this lecture honoring such a distinguished scientist in American history.

Opportunities and Responsibilities in International Health

Today, the focus in teaching and research in the health sciences has swung to the United States as a result of an unprecedented mobilization of manpower, facilities and funds for training and research in the last fifteen years. With this has come an awakened recognition of our opportunities and responsibilities to share our knowledge and skills with other nations—that in the field of health, we speak a common language and share a common bond of friendship; and, equally important, although we have much to give, so, too, do we have much to receive—the teacher becomes the taught.

Our opportunity and responsibility to put science and technology into practice in the interest of human health around the world is emphasized especially in the developing countries. Many nations have only recently won their independence. Their leaders know they will fail their people unless they improve the conditions of life. The majority of these people eke out a bare existence under tremendous handicaps of hunger, disease and early death. They are aware that, for some people, the good life is a reality and that it could be for them, too. They need desperately the encouragement and neighborly help of the stronger nations of the free world—hungry and sick people do not distinguish clearly between different political and economic systems—they are not as concerned with freedom of speech, of assembly, and of worship as they are with food to prevent

[1] Arthur Parker Hitchens Lecture VI, College of Physicians of Philadelphia, 21 November 1961.

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starvation and medicines to cure disease and prevent death.

Putting our knowledge and know-how to work for the people of these nations gives real meaning to our utterances about the dignity and worth of the individual. At the same time, it extends understanding between individuals —a first step in promoting understanding between nations.

Health is a force in international life for new areas and techniques of cooperation. It is a rallying point of unity, around which men of differing languages, cultures, and faiths can define needs and goals, and then pool their brains and resources for the human being everywhere.

There is no competition in the struggle for better health. In the process of gaining health, no nation takes it away from another—on the contrary, it helps advance health throughout the world.

Maps charted of the oceans in the International Geophysical Year show more clearly than words can tell that continents and even the most remote islands are united by solid ground, at depths which are shallow in comparison with the heights man is achieving in outer space. This union under the seas and oceans clearly emphasizes that our international obligations are really extensions of our local responsibilities.

Major Health Problems in the Developing Countries

Malaria, now banished from the North American continent, is probably the most widespread of maladies the world over. Ten years ago, it claimed over 300 million victims and resulted in 3 million deaths annually. In addition, it rendered vast areas of fertile land unfit for habitation and was an insuperable obstacle to progress and prosperity in many countries. As a result of an intensive world-wide attack on malaria, both the number of cases and number of deaths have been cut in half. In addition, millions of acreas of land have been made inhabitable. Rice production in the Philippines is sufficient for the first time in the history of the Islands to meet their needs with a 20 per cent increase in rice acreage due to a vigorous malaria program. Millions of acres in India are now available for agricultural purposes, previously uninhabitable because of malaria.

A gigantic, world-wide malaria eradication program is in progress, in contrast with simple control—with direction from WHO, and major support from our country through AID. Haste is essential to effect eradication before the mosquito develops resistance to present known insecticides, chiefly D.D.T.

Filariasis, sometimes called "river blindness," is transmitted by a gnat which breeds in rapidly flowing streams. It impairs vision and may cause blindness. Twenty million people are affected in Africa, Central and South America.

Schistosomiasis, transmitted by a species of snails, affects about 150 million people in tropical and subtropical countries. It results in prolonged disability and is, therefore, a serious economic problem. Egypt is rapidly expanding its irrigation projects to reclaim land for food production. But these very irrigation canals contribute to the spread of schistosomiasis, and the disease is a major deterrent to agricultural progress.

Trachoma, a viral disease of the eye often leading to blindness, has been eradicated from the United States except for a few small foci in the American Indians of the Southwest. It is a major problem in other parts of the world, however, affecting about 400 million people, 10 million of whom will become blind. This is a disease associated with poverty, poor sanitation and ignorance. In some sections of Africa the entire adult population suffers from the infection.

Tuberculosis, under increasing control in our country, still afflicts millions of people throughout the world. In the past 10 years, approximately 100 million young people in 58 countries have been vaccinated with BCG vaccine under the auspices of WHO and the UN Children's Fund, in addition to the administration of the newer anti-tuberculosis drugs.

The tsetse fly, spreader of African sleeping sickness, has left 4,500,000 square miles of land in Africa almost totally idle—waiting for control of this vector to become the world's largest reclamation project.

Leprosy, cholera, the dysenteries and other infectious and parasitic diseases haunt the developing nations of the world and stand in the way of their health and progress.

Suppose we narrow our focus on a single country—the newborn and deeply troubled Republic of the Congo. Its recent transition from underdeveloped territory to underdeveloped independent nation has been marked by unusually severe birth trauma. What we know of its health problems and resources is both instructive and sobering.

It lies in equatorial Africa—its area is about equal to that of the United States east of the Mississippi—its population is about 14 million. The following conservative data conveys some impression of the magnitude and diversity of the health problems of the Congo:

Smallpox	25,000 cases reported in a 6-year period
Tuberculosis	32,000 cases reported in 1957
Amoebic dysentery	159,000 cases reported in 5 years
Hookworm	320,000 cases reported annually
Venereal diseases	245,000 cases reported in 1957
Leprosy	271,000 cases reported in 1957
Yaws	170,000 cases reported annually
Malaria	945,000 cases, 2,300 deaths, reported in 1958
Schistosomiasis	80% prevalence reported in parts of Katanga Province.

In addition to these and many other infectious and parasitic diseases, nutrition is a serious problem. The native diet is deficient in proteins, especially animal protein. The combined intake of all meat, fish, eggs, milk and dairy products adds up to less than 2 per cent of the daily caloric intake.

In the transition to an independent Congo, the World Health Organization responded swiftly and effectively in the emergency—a highly dramatic demonstration of this organization's ability to respond to a local crisis. And yet this temporary regimen is the thinnest kind of cover over a gaping chasm of need. Where are the resources to come from—manpower and facilities—to make a genuine impact on the health problems of the Congo and elsewhere in the developing countries?

Most of the widespread diseases of the underdeveloped countries—malaria, schistosomiasis, trachoma, leprosy and others—are chiefly disabling diseases. The first result of their control is not the addition of many more mouths to feed, but rather, many more hands to work.

Truly, the introduction of a well man into an economy does not create problems—it solves them.

Malnutrition

Malnutrition is a major public health problem in most of the economically underdeveloped countries. One does not have to look far to find the reasons for this. Agricultural practices in most of these countries are primitive, with the result that food production is not commensurate with the nutritional needs of the population. The people, in general, are poor and largely illiterate. Relative unavailability of protective foods, poverty of the masses, and ignorance fortified by practices originating in social background and cultural traditions contribute collectively to the wide prevalence of undernutrition and malnutrition.

A variety of soil and climatic conditions is responsible for different types of food crops and other foodstuffs grown in different developing regions of the world. One thing seems to be common to most of them: available sources of animal foods such as milk, meat, eggs and fish are meager or are not adequately

utilized and hence find a comparatively insignificant place in the dietaries of the people. Similarly, the production and consumption of vegetables and fruits are inadequate. It is small wonder then that carbohydrate-rich dietaries based on cereals, tubers and bananas not properly balanced with protective foods should result in such widespread malnutrition as is being encountered today in these countries.

The types of malnutrition which exist in different parts of the world differ to a certain extent with dietary habits. For example, beriberi, which occurs in certain countries of South East Asia, is associated with the consumption of polished rice, and pellagra in Africa is associated with the consumption of maize as the staple of diet.

However, there are some common underlying conditions which are responsible for a much wider occurrence of certain types of malnutrition than these two examples given above. In almost all developing countries around the world infants and young children suffer during or after weaning from two extreme forms of malnutrition: undernutrition leading to nutritional marasmus, and protein malnutrition resulting in the well-known syndrome, kwashiorkor. Unavailability of cow's milk, underfeeding, and defective feeding with protein-poor foodstuffs during the course of weaning are principal factors responsible for the occurrence of these conditions.

The significance of protein-calorie malnutrition as a world problem has emerged largely as a result of activities of WHO and FAO. Both these organizations are now engaged, with the help of UNICEF, in devising measures for its control and prevention.

Population Problems

It is true that the population explosion in these countries continues to create a very serious problem. I had the pleasure of visiting Prime Minister Nehru during a recent visit to India. He asked what criticisms and suggestions I had of their research and public health programs. My reply was that they were doing well with what they had, but needed more of everything. His reply was, "Yes, more of everything but people." They increase their food products by 3½ per cent and this is absorbed by an equal increase in population. They increase their electrical output by the same amount, and this is absorbed by the exploding population. So they are running hard just to stand still! Family planning is an accepted program in India, but is not effective at present because of the lack of an effective agent, and the development of an effective educational program to reach all the people.

Health Manpower Needs

All of these countries are deficient in health personnel. They are particularly anxious to have the assignment of teachers and health personnel from America, both to assist in training their own people and to provide essential and badly needed services until they become more self sufficient.

Everywhere one finds the greatest admiration and respect for the American health professions and for what they are doing in teaching and research. Many nationals from other countries, of course, have been trained in our institutions. Thousands more would like to come for such training. Since English is spoken by about 500 million of these people, language is no barrier for this kind of interchange.

Contributions of Religious Groups and Foundations

One finds everywhere the physical evidence as well as the educational results of the tremendous contributions that various foundations and religious groups have made from the United States in all of these countries. When we talk about American aid to the developing countries, we are inclined to think primarily of governmental aid, which, of course, has been a real factor in the last several years. But, many years before this, medical schools, hospitals, nursing schools, research

institutes and training were stimulated and assisted by foundations and religious groups. These have made a real impact on the countries and have left an indelible stamp on not only the health services, but also in the attitude of these people toward the United States.

The program of the U. S. Agency for International Development (AID), formerly the International Cooperation Administration (ICA), throughout its health missions, has been of great value in providing training, technical assistance, and financial support in such areas as medical education, hospital construction, malaria eradication and nutrition. I have never met any of the individuals assigned to these missions, regardless of the isolation of the post or the hardships of the environment, who did not return with a real sense of having accomplished something worthwhile, often actually disliking to leave because of the great unfinished task. The life of many of these people, together with their wives and children, is not an easy one, regardless of what anyone might say. Some of the criticism may be justified as it relates to the use of funds, but I believe that criticism directed at the people of these missions is by and large unjustified. It is probably made by individuals who spent a few days to a week in a modern hotel in the capital city and who have not had to live from two to four years in some of these places under circumstances of housing, schooling and sanitation which are so foreign to what we are accustomed.

The Challenge

The levels of expectation of people everywhere are rising. The underdeveloped nations are the developing nations—their people are no longer satisfied with things as they were or as they are. Their aspiration is the hope of the future and the challenge of the present for nations like ours.

Better health for its own sake is among the benefits desired and expected. It is also an essential resource for the realization of other goals and aspirations. As we assist them in fulfilling their expectations of better health, we contribute to the fulfillment of their expectation of us. We are contributing to their capacity for self-fulfillment in the future. In so doing, we are sowing fertile seeds of understanding and a sense of union with our fellow men in our shrinking world community.

Can a democracy like ours successfully meet the challenge and the opportunities required to assist these young and struggling emerging nations? Can our society, which treasures the freedom of man and believes that man is the master and not the servant of government, rise to our responsibilities in helping these countries in their life and death struggle? Freedom and peace are the very foundations of these struggles for survival, and our free society and its democratic institutions are on trial. Can we meet successfully the challenge of a highly competitive, highly organized central authority?

A Greek philosopher, believing that the fall of Athenian democracy resulted because only a few were educated, made this statement: "The State says that only free men shall be educated; God says only educated men will be free." We might add, ". . . only educated and healthy men will be free."

Pooling of the world's scientific resources for the betterment of human health ranks with the great challenges of our time: nothing holds higher drama or greater promise than a truly international crusade for health, a road to a just and lasting peace.

Conclusion

Our country and the whole world greatly need men of the caliber of Arthur Parker Hitchens, men with vision and imagination and the vigor and enthusiasm to make dreams become realities.

Pasteur said, "There is science and the application of science, bound together as the fruit to the tree that bears it." So, too, is the world community of scientists even more bound together in a common quest for knowledge and the action to put that knowledge to

work for the benefit of mankind everywhere. We honor Dr. Hitchens and his colleagues when we carry on that which they so well began, using the health sciences as a common bond with our fellow scientists in all nations of the world. The task is great, but not impossible. The rewards will be not only a better life for all peoples, but understanding and goodwill, so essential to peace with justice and progress.

Better Health for Americans: The Need for Standards of Medical Care[1]

By DAVID D. RUTSTEIN, M.D.[2]

A STATEMENT frequently appears in the public press, usually made by an official of the American Medical Association, that the United States of America has the best medical care and is therefore the healthiest nation in the world. What does this statement mean?

The best medical care implies that all existing scientific knowledge is applied in the most effective way to prevent and treat disease and disability, and to postpone untimely death. To attain this objective, each personal physician and specialist must have and use optimal medical facilities, i.e., laboratories, hospitals, nursing homes and ancillary medical services such as physiotherapy, public health nursing and medical social service. The personal services of physicians must provide for continuity of care and correlate the many facets of care needed at any particular moment by any patient. If "the best medical care" is then combined with a public health program which includes environmental sanitation, we might be the healthiest nation in the world with the least illness, the smallest proportion of disabled people and the longest life expectancy.

How can we tell whether we do meet such criteria? We cannot count all of the different kinds of sick people in every country of the world. There is little use in knowing how many doctors are available to our population. In 1910, at the time of the Flexner Report when medical care was very poor, we had a higher ratio of doctors to patients than we have now. Moreover, methods have not yet been developed for comparative measurement of the quality of care provided by the average physician throughout the world.

There are two indices, crude as they may be, which have been helpful in approximating the health of a population—(1) Life Expectancy at Birth, and (2) The Infant Mortality Rate. Although frequently used, a third important index, the Maternal Mortality Rate, proves not to be very good because of the way physicians fill out death certificates, and health departments tabulate them. Only the direct maternal causes of death tend to be noted and tabulated. It is therefore practically impossible to determine the total impact of maternity on the death rate.

Where do we stand in life expectancy at birth? According to the 1960 Demographic Yearbook of the United Nations[1], the United States stands 13th in the list of countries of the world for life expectancy at birth among males (Table I) and 6th for life expectancy among females (Table II). Norway heads both of these lists, and is closely followed by The Netherlands and Sweden in alternate order for each of the sexes. More important, within the United States, there are wide differences dependent upon such factors as color and geography. Thus for the year 1959 in the United States[2], the life expectancy at birth of white males was 67.3 while that of non-white males was clearly shorter—60.9 years. For females the indices are 73.9 for whites and 66.2 years for non-whites.

Life expectancy varies from state to state[3] with the longest life expectancy of white males for 1949–51 in South Dakota of 68.4, and the shortest in Nevada of 62.8 years. For females, the longest is 74.0 in Nebraska, and the shortest 69.1 years in New Mexico. For Pennsylvania the comparable figures are males 65.9 and females 71.0, both in the lowest

[1] James M. Anders Lecture XLI, College of Physicians of Philadelphia, 1 November 1961.

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third of the States of the Union. Thus, using the index of life expectancy at birth, we stand fairly high among the countries of the world although we would certainly not be classified as "the healthiest," and there are wide variations within our own country.

The Infant Mortality Rate, i.e., the number of infants out of every thousand born alive who die under one year of age, is an even more sensitive index of the health status of the population. This is so because this rate can be directly affected by changing living and sanitation standards, better maternal care, more careful pediatric supervision and medical care during the first year of life. According to the World Health Organization's Epidemiological and Vital Statistics Report (1961)[4], the United States' infant mortality rate of 26.4 per thousand (Table III) ranks 11th among nations of the world. Sweden has the lowest rate (16.6) and is closely followed by The Netherlands and Norway. Thus, we are far from "the healthiest nation in the world" insofar as infant mortality is concerned.

Within the United States, there are marked and serious differences between infant mortality rates from place to place and from group to group. Thus, by States, in 1958, the infant mortality rate among whites[5] was lowest in Rhode Island (20.0), highest in New Mexico (33.3), with Pennsylvania having the low white infant mortality rate of 22.9. It is interesting to note that the rate among whites in our State of lowest infant mortality—Rhode Island (20.0)—is higher than the total rate for Sweden of 16.6. Infant mortality rates among non-whites in the United States have always been higher—in 1959—44.0 as compared with 23.2 for whites.[6] The range of non-white rates varied in 1958 from a low of 29.0 in Minnesota to 72.8 in New Mexico,

TABLE I

EXPECTATION OF LIFE AT BIRTH
MALES

Country	Year	No. of Years
Norway	1951–55	71.11
Netherlands	1953–55	71.0
Sweden	1957	70.82
Israel (Jewish Pop.)	1959	70.23
Denmark	1951–55	69.87
New Zealand (European Pop.)	1950–52	68.29
England and Wales	1959	68.1
Canada	1955–57	67.61
Northern Ireland	1957–59	67.44
Czechoslovakia	1958	67.23
Australia	1953–55	67.14
West Germany	1958–59	66.67
United States	1958	66.4

Source: Statistical Office of the United Nations. *Demographic Yearbook 1960.* 12th Edition, 621 pp. New York: United Nations, 1960.

TABLE II

EXPECTATION OF LIFE AT BIRTH
FEMALES

Country	Year	No. of Years
Norway	1951–55	74.70
Sweden	1957	74.29
Netherlands	1953–55	73.9
England and Wales	1959	73.8
Canada	1955	72.92
Australia	1953–55	72.75
United States	1958	72.7

Source: Statistical Office of the United Nations. *Demographic Yearbook 1960.* 12th Edition, 621 pp. New York: United Nations, 1960.

TABLE III

INFANT MORTALITY RATES*
1959

Sweden	16.6
Netherlands	16.8
Norway	18.7
New Zealand (excluding Maoris)	19.9
Australia	21.5
England and Wales	22.2
Switzerland	22.2
Denmark	22.5
Finland	23.6
Czechoslovakia	25.8
United States	26.4

* Deaths under one year per 1000 infants born alive. (Excludes European population of Federation of Rhodesia and Nyasaland.)

Source: World Health Organization, *Epidemiological and Vital Statistics Report, 14:* No. 6, 1961.

with Pennsylvania about half-way in between (47.7).

Until recently we were encouraged by the more rapid fall in the infant mortality rate among non-whites as compared with whites. This led us to believe that the rates would eventually reach the same level. But in the early 1950's, according to a recent report by Moriyama[7], a striking change occurred. The downward trend slowed for both groups, but the effect was more marked among the non-whites so that at the present time, the gap between infant mortality rates for the two groups grows wider year by year. This effect is seen vividly in your own State. Pennsylvania now actually has a rising infant mortality rate for non-whites (43.0 to 47.7 from 1954–58) while the white rate has levelled off (23.1–22.9 over the same period).[5]

It is clear that the statement, "We are the healthiest nation in the world", is not supported either by analysis of life expectancy or of infant mortality. Indeed, there are no data to justify the statement. But, even if we assumed that this statement were true, the health status in certain geographical areas and groups in the United States is far below that attained in other regions and groups in our country. There is therefore much room for improvement. There is also the constant challenge of the expanding reservoir of scientific knowledge, skills and facilities which should lead to better medical care and a constantly rising level of health for all of our citizens.

What can be done, then, about improving our health status? First, we can try to find the reasons for differences in the indices from country to country and in different parts of our own country with the expectation that some of the evident defects may be repaired. Second, it is possible, as I will demonstrate, to look at the rapidly increasing body of scientific medical knowledge, the pool of constantly improving medical skills, and the burgeoning mass of medical facilities and community resources and establish measuring sticks to determine how well the medical care provided in a given area approximates the ideal. With such standards and the results of studies now under way, organizations such as the College of Physicians of Philadelphia could provide the necessary leadership for improving the health status of the United States.

The Department of Preventive Medicine at the Harvard Medical School has been actively concerned with creation of measures of quality and of standards for the improvement of medical care. For example, a comparative study with Swedish and British investigators and with the Health Information Foundation is now under way under the direction of Dr. Osler L. Peterson. This study is planned to measure the impact of health services on carefully sampled population groups in the three countries, so that it may be possible to determine the reasons for inter- and intra-country differences in health indices. Practical results from these studies may be expected. For example, Sweden, which has excellent health indices, has a much lower average physician-patient ratio than we have in this country. We have been struggling to expand our medical educational facilities to maintain our present ratio of one physician for every 750 in the population while Sweden apparently gets along better with less than one physician for every 1200 of its population.[8] This lack of correlation of health indices with the physician-patient ratio is found also within the United States, i.e., South Dakota with the longest life expectancy for white males (68.4 years) has the lowest physician-patient ratio in the United States (1/1400).[9]

The studies now under way should yield precise data on the important question of the relationship of physicians' services to the health status of the population. It is clear that the prevention of disease by an improved water supply does not depend on the availability of a physician. At the other extreme, a physician can save life through the emergency treatment of acute congestive heart failure or the surgical treatment of acute appendicitis. In between these two extremes, there is an

increasing gradient of the contribution made by the physician to the health of his community. Many years ago, Professor Lawrence J. Henderson expressed the opinion that it was "probably true to say that a random patient with a random disease consulting a doctor chosen at random stood better than a 50/50 chance of profiting from the encounter."[10] Today, the problem is much more complex. The physicians' tools are now more specific and more helpful. But, they have also become more powerful and if used improperly by physicians they may present an actual danger to the patient. As a result, we hear more and more about iatrogenic disease. Moreover, medical advances are appearing at such a rapid rate that a physician ten years out of medical school must practice a brand of medicine which was unknown at the time of his graduation. If the physician is to meet his responsibility on the one hand of doing no harm—"primum non nocere"—and on the other, of improving and maintaining the health of his patients and of the community, current medical standards combined with an effective postgraduate education program become essential.

The development and use of standards of medical care have been under study in our department since 1947. Students at the Harvard Medical School are required, in the summer between their third and fourth years, to conduct and report on a health resources survey of a community. The principle objectives of the health resources survey are to make the student aware of his responsibility for providing for his patients the highest possible quality of medical care in his community within such limitations as income, geographic location, education of the population, and accessibility to a medical center. To do this, he must recognize existing assets and deficiencies in medical care and devise practical means for their elimination or for their improvement. As a future physician, he is expected to demonstrate a thorough understanding of community health resources since their effective use and constant improvement is essential for the practice of good medicine.

In making the survey, each student is asked to imagine that he has just completed his formal period of medical education and has entered into practice in a community of his choice. He is given the case histories of four seriously ill patients who might seek his help in his first week of practice. These case histories are selected so as to cover the range of all commonly used medical resources, extending all the way from the availability of a qualified consultant in a specialized field of medicine, through the use of a hospital, laboratory or nursing home, to ancillary medical skills such as physiotherapy, public health nursing, medical social service and including all of the economic and social facilities that might be needed to give the patient complete medical care.

The student first prepares a statement of optimum resources for the care of his patients based on existing scientific knowledge, medical skills and medical and social resources. He then goes to a community of his choice, assumes that he is the responsible physician and collects and records quantitative and qualitative data about the actual personnel, organizations and services available for the care of these patients. The data on actual facilities and services are then compared with his statement of optimal resources. The student prepares a report stressing the differences found and makes practical recommendations for repair of the deficiencies and for improvement of the quality of medical care in the community.

The details of this survey method may be reviewed in the Instructions to the Students and the Case Histories for 1961 (Appendix A). These cases cover the entire gamut of health and medical services. The student's analysis of discrepancies between optimal and actual facilities supported by a statement of practical recommendations delineates the most effective channel of care for each patient.

Our experience during the last 14 years with this teaching exercise convinces us that with

minor modifications it could be extremely useful to any community interested in appraising its own health and medical resources. Indeed, surveys done by the students have already been used for this purpose in communities in many parts of our country. Recently one community found the student's survey more useful than the expensive evaluation of health resources performed by a firm of management consultants. The reasons for the greater usefulness of the student's survey are obvious. Management consultants usually limit their studies to the efficiency of the "medical care machine", i.e., they count the number of full and empty hospital beds and decide how well they are used, or they study the personnel in the laboratory in terms of the number of tests turned out per unit of time. In contrast, the students not only appraise the "medical care machine" but assay its effect on the patients and on the community. They look at the final product—medical care—and ask the crucial question—Can we do away with unnecessary disease, disability, or untimely death?

This evaluation method can be used by a professional organization such as the College of Physicians of Philadelphia for appraisal of the medical care program and the health status of its particular community. In doing so, minor modifications are needed because our students search for the best channel of care in the community for their own patients. In the appraisal of the total medical care and the health of a community all of the usual channels of care will have to be explored. In other words, the same comparisons will have to be made for all of the major channels of care.

In performing a survey, the conventional measuring sticks of life expectancy at birth and infant mortality rate will be helpful but, in addition, local indices of health will have to be created dependent upon the number and kind of major defects discovered. Also, national standards such as those used for the qualification of medical specialists, for ancillary medical personnel or for the accreditation of hospitals or clinics must be examined in the light of their effects on community health and medical care. Information so collected in a community such as Philadelphia will then be very helpful in improving national standards for use elsewhere.

In any evaluation comparing ideal and actual facilities, provision has to be made for constantly raising the level of optimal facilities as medical research increases our reservoir of knowledge, and as personnel and facilities improve and expand. Each community will then have a sound and changing goal as it maintains within practical limitations the highest possible standard of medical care. For nationwide use, agreement will have to be reached among communities so that results may be comparable.

Medical standards have another use. As the cost of medical care continues to rise rapidly, grave economic problems follow in its wake. According to the Wall Street Journal for June 9, 1961, states such as Colorado and New Mexico have arbitrarily limited medical care benefits for the aged based on available funds rather than medical needs. In my own view, a modern civilized society must place a high enough premium on good medical care so that any scientific knowledge, professional skill or resource which can preserve life or prevent or cure disease will be available to our citizens. Indeed, our advice to under-developed countries often takes this form. But, if we really decide that the total cost of medical care exceeds our assets, a decision to limit benefits must not be based on a first come, first served basis until the appropriation of funds is exhausted. Rather, with the use of standards, intelligent priorities can be established as to the most effective use of available funds in the preservation of life and in the prevention and treatment of disease.

I am informed that your Mayor, Mr. Richardson Dilworth, reacting to a crisis at the Philadelphia General Hospital, paraphrased Clemenceau to say that the "health of the people was too important a matter to be left to physicians alone." Mayor Dilworth's state-

ment has a clear implication for our present discussion. As more and more lay influence makes itself felt in the complex mechanism of providing medical care, informal standards are automatically created. Every piece of medical legislation and every health insurance contract indirectly imposes informal standards of care not based on scientific medicine. Thus, a medical insurance contract is considered satisfactory if the clause providing that the first fifty dollars of the cost of each illness is paid for by the patient, is successful in limiting the number of claims. It would seem important first to determine whether the "deductible clause" will lower the quality of medical care, for example, by a delay in the diagnosis of early cancer. Since the medical need must take precedence over the economic one, it becomes imperative that leading organizations of the medical profession such as the College of Physicians of Philadelphia immediately undertake to establish standards of quality and quantity of medical care for the guidance of the medical economist or actuary. It is no longer enough for the spokesman of the physician to repeat the clichés that we have the best medical care and that we are the healthiest country in the world. If the medical profession does not assume this leadership, laymen will eventually completely take over this responsibility.

The College of Physicians of Philadelphia can make its own contribution to the health of the Nation. It should examine its community through the use of existing indices and available standards, and it should study its health resources scientifically by matching them against optimal facilities. From such studies, immediate improvements can result and long-term health goals for Philadelphia can be firmly established. Such professional leadership would improve the quantity and quality of medical care and elevate the level of health in Philadelphia in a way such that the results could be measured, standards set, and the benefits applied in other communities in all parts of the country.

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APPENDIX A

Harvard Medical School, Department of Preventive Medicine
Instructions for Performance of Health Resources Survey, 1961.

This survey is designed as an exercise in the application of the principles you have learned in medical school to the care of four hypothetical patients in a community of your choice. The survey will be the basis for your fourth year grade in Preventive Medicine. In the medical school curriculum, 50 hours of credit are allocated for this survey.

Up to this time you have been learning to become a physician in a medical school and teaching hospitals where more and better resources exist for the care of patients than you are likely to find in the average community. The principal objectives of this survey are to make you more aware of your responsibility to provide the highest quality of medical care possible for your patients under the conditions existing in your community and to encourage you to consider practical means for improvement. We expect you to demonstrate

an adequate awareness and thorough understanding of community health resources since this is essential for the practice of good medicine.

A brief medical history and pertinent physical findings in each of four cases are attached along with some additional information about prognosis and socioeconomic status. You are to prepare a detailed statement of the diagnostic, therapeutic, and *preventive* resources that you would require for the optimal management of each patient. These should not be limited to the obvious ones provided by a physician in a general hospital but should include all those institutional and community resources which might be used to improve the status of the patient. Thus, a patient suffering from tuberculosis might require the services of a general physician, a specialist, public health nurse, medical social worker, occupational therapist, special hospital, facilities for convalescent care and perhaps vocational guidance. Preventive services are to be outlined from the point of view of preventing disease, complications, and disability or death of the patient. In addition, discuss in each case measures which might have been instituted prior to the development of disease which might have been of some help.

Following the preparation of the statement of optimal resources, you are to go to a community of your choice to collect and record data about the personnel, organizations, and services that actually exist for the complete management of the four cases. In each case assume that *you are the responsible physician* and indicate how you would make the best use of the available resources. It is expected that you will show evidence of a thorough understanding of the type, quality and scope of the required services as well as the means for their implementation. In general, the two most useful methods for obtaining information about the medical assets of a community are (1) personal interviews with physicians, hospital administrators, public health officers, and other representatives of governmental and voluntary agencies in the health and welfare field, and (2) reference to published material such as that dealing with the qualifications and number of physicians, classification and description of hospitals, medical care plans and welfare agencies. It is desirable to use more than one source of information in your evaluation since a critical appraisal of the quality of medical care cannot be accomplished without comparisons of facts and opinions. Document the sources of information by listing the names of all individuals or agency representatives interviewed. You are not required to prepare a complete analysis to all community health assets but rather you are expected to find the *best channel of care for your patients* in view of the most probable diagnosis in each case.

Finally, you are to compare the conditions existing in the community with your statement of optimal resources and to write a critical discussion of the differences. It is expected that you will relate your recommendations to existing community agencies or those which might be developed. You should not recommend an unattainable Utopian situation.

An introductory section should provide a general description of the community and its resources, with reference made to those personnel, agencies and services to be used in the management of the four cases. Then each case should be presented as a unit, clearly indicating the specific application of the resources to each patient. Your recommendations should be numbered so that they may be readily identified by the reader.

Thus, your survey report will include:

1. Introduction
2. Optimal resources
3. Actual resources
4. Differences and recommendations.

Your survey report must be received by the Department of Preventive Medicine prior to *September 5*, 1961. The report should be typewritten (double-spaced), paged, and bound. Please show your name, the locality surveyed, and the date of the report on the outside cover of your paper.

Since the report will go on permanent file and will not be returned to you, it is recommended that you keep a copy for your own records. It is also recommended that, if possible, the survey be done by pairs of students.

Following the submission and evaluation of your report, arrangements will be made for a conference between you and a faculty member to discuss the survey.

Health Resources Survey 1961

Case I

You are called by a neighbor to see a 71-year-old spinster who has been unable to get up out of bed for the past three days because of shortness of breath.

On visiting the old lady in her third floor walk-up apartment, you note that the room is untidy and that the furnishings are in disrepair. The patient is lying in bed propped up on 3 pillows, breathing rapidly.

The history of the illness is difficult to obtain because of deafness. The patient had begun to notice difficulty with her hearing at age 50 years. The hearing loss was associated with tinnitus without vertigo. There is a family history of deafness in the mother and one sister, both of whom died at age 68 years with a "shock." The patient states that she has noted increasing shortness of breath and weakness the past week. She had been taking "heart pills" intermittently for three years. She has been unable to get out of bed the past three days because of shortness of breath, weakness and pain in her knees, elbows, wrists and hands. She has been troubled with pain and stiffness in her joints for the past 10 years and this discomfort has been partially

relieved by aspirin. There is no history of exertional chest pain, heart murmurs or hypertension.

Physical examination: T = 99.4°, BP = 186/86, P = 110, R = 28/min. There is an obvious deafness, more severe on the left than on the right. There is no localization of the sound of a tuning fork placed on the vertex of the head. Bone conduction is no better than air conduction. The tympanic membranes are white, lacking in luster and slightly retracted. Ophthalmoscopic examination reveals grade 1 changes of arteriolar narrowing and tortuosity with dull appearing vessels. The head and neck are otherwise normal.

Examination of the chest reveals moist rales at both bases extending up to the angles of the scapulae. Respirations are rapid and somewhat labored. The neck veins are distended up to the angle of the jaw. The P.M.I. is visible and palpable in the anterior axillary line. Rhythm is grossly irregular. There is a pulse deficit of 6 beats per minute. No murmurs are audible. The liver edge is palpable 4 cm. below the right costal margin and slightly tender. There is a 2+ pitting edema of the pretibial region and over the sacrum. There is no cyanosis. The skin is pale and moist.

Examination of the extremities reveals deformity of the proximal and distal interphalangeal joints and slight ulnar deviation of the fingers at the metacarpophalangeal joints. Motion of the hands in flexion is markedly limited. There is no redness or increased heat. There is some deformity of the elbow joints with inability to extend the joint completely and marked limitation in supination. The knee joints have fusiform thickening; there is inability to extend the joint fully and some muscle atrophy of the quadriceps bilaterally.

The patient lives alone, and is assisted by neighbors who do her shopping for her from time to time. Rental on her apartment is $70 per month. She has an unmarried nephew who visits her about once a month. She has no other living relatives. She lives on Social Security benefits and her savings which have now dwindled to $857. She has been reluctant to purchase "expensive medications" because of her meager resources and has refused attempts to be provided with public assistance because she considers this "charity." Until she became too old to work, she had been employed for twenty years as an office worker earning $50–75 per week.

Case II

You are visited in your office by a 38-year old lawyer who is concerned because of a mass he has discovered in his neck. He first noted a mass of "glands" in the right side of his neck three months previously. This has enlarged noticeably in the past two weeks, and at his wife's urging he decided to take time off from his busy law practice to look into it. He has not been alarmed about the mass because it had been non-tender and painless. There is no history of any weight loss, fever or sore throat. He has had no recent illness of any kind. He has not seen a physician in four years.

On physical examination, you note a well nourished, carefully attired man who does not appear ill, but looks worried. There is an obvious mass, 8 cm. in diameter, on the right neck which appears to be made up of firm, matted, adherent posterior cervical lymphnodes. There are no lesions in the pharynx or on the scalp and the thyroid appears to be normal. A similar group of firm, confluent nodes is palpable in the left axilla. There are several discrete lymphnodes palpable in both inguinal regions. None of the nodes palpated is tender or fluctuant. The liver and spleen are not palpably enlarged, and the skin is normal.

Complete blood count and chest x-ray done the following day are entirely normal.

The patient lives with his wife and two children, aged 4 and 8, in a heavily mortgaged $45,000 home in the best section of town. His income last year was approximately $20,000 before taxes. He drives a small foreign car, and his wife drives a Mercury station wagon; both are to be paid for within two years. He has recently enlarged his law offices and has taken in a partner. He has a $10,000 term insurance policy which he has maintained since discharge from the Army. He also has a $30,000 Straight Life Insurance policy. He has no disability insurance. But he does have Blue-Cross Hospital Insurance. His 8-year old daughter goes to a private school. She is having her teeth straightened by an orthodontist. He belongs to the local country club.

For purposes of discussion, assume a life expectancy of three to five years.

Case III

You are called to the local hospital to see a 24-year old cab driver who was just brought in by a police prowl car.

The history, obtained from the officer, indicates that the patient's cab was struck by an oncoming car while he was making a sudden, unsignaled U-turn to pick up a fare. The driver was thrown out of the cab and, when first seen by the officer, was lying on the ground unconscious. The officer lifted him into the prowl car and drove him to the hospital immediately. The officer believes the driver was unconscious for about 5 minutes.

On examination, you observe an apprehensive, confused, pale young man complaining of headache and pain in his left arm. He cannot recall any of the events leading to the accident. On examination, his left arm is noted to be excruciatingly painful and it is necessary to cut the left sleeve out of his jacket. Examination of the arm, which he holds adducted and supported by his other arm, reveals swelling, shortening, and lacerated skin pierced by fragments of bone at its proximal third.

General examination: BP = 198/64, P = 110, R = 28, T = 98°F. (Oral).

The skin is pale, moist, and cool. The funduscopic examination is normal. Pulse is rapid and feeble but palpable bilaterally at the wrist. Pupils are regular and equal and react to light and accommodation. The neck is not rigid. There is no drainage from the nose and ears. There is no swelling or tenderness over the mastoids. No tenderness, depressed areas, or lacerations are noted in the scalp. There are no localized neurological findings.

Examination of the heart, lungs, and abdomen reveals no abnormality. The remainder of the extremities and the back are normal.

Examination of the spinal fluid reveals normal manometrics and microscopic findings; the spinal fluid protein is normal.

Two weeks after the injury, the patient still complains of headaches, "dizziness," inability to concentrate, and nervousness. He also says that he sleeps poorly, is easily fatigued and feels depressed. He is unable to tolerate noise, crowds, or excitement. He still has some amnesia for the events leading to the accident and the period immediately following. The wife states that the patient's nervousness is not a new symptom but that it has probably been aggravated since this injury. She also informs you that he has usually worried about his health and about family finances.

He is employed by a small taxi company run by the owner of a local garage. The company operates two cabs with four drivers. The patient earns up to $90 per week. The patient has a wife and two children, aged 1 and 3. The wife has a high school education and no training for any type of employment. The family lives with the wife's mother. They have themselves remodeled the second floor of her rather small house into an apartment for which they pay a rent of $45 per month. This payment is an important contribution to the mother's support. Living with the mother has involved some strains and disagreements. Careful management has allowed them to save about $650. They intend to use this to make a down payment on a home of their own. They have Blue Cross hospitalization insurance.

Case IV

You are called to see a 7-day old infant discharged the previous day from the hospital nursery who has developed a skin rash, fever and refuses to nurse adequately. The infant was delivered without difficulty after an uneventful full-term pregnancy. He weighed 6 lbs. 11 oz. at birth and now weighs 6 lbs. 3 oz.

Examination reveals a listless infant, crying feebly. There is a vesico-pustular eruption on the face and scalp. The lesions consist of flat erythematous macules and superficial vesicles. Also present on the abdomen is an inflamed area and serous discharge about the stump of the umbilical cord. The infant's skin and mucous membranes are dry.

Temperature 101° rectal, Pulse 140, Respirations 28. Lungs are clear to auscultation and percussion and the heart is within normal limits. Examination of the abdomen is normal except for the umbilicus. The liver is palpable one finger breadth below the right costal margin, and the tip of the spleen is palpable.

The 36 year-old mother has been nursing the infant and appears entirely well. But three days after your first visit, she developed a tender painful area in the left breast just lateral to the areola, and a slight temperature elevation. In spite of treatment, after five more days the breast lesion progressed to a tender fluctuant mass. Cultures of the skin lesions and area of the umbilicus yield coagulase positive staphylococci resistant to penicillin-G.

The infant has 4 brothers and 2 sisters, ages one to 14 years. The father is a gas station attendant, his fourth job in six years. He has had a high school education but no special training or experience in any trade. The family has no medical insurance, and lives in a heavily mortgaged 6-room frame house which is quite run down owing to lack of proper maintenance. The husband is known to indulge in sporadic alcoholic excesses. The family is well known to the Welfare Board and to charities affiliated with the church. The oldest daughter, age 14 years, has been looking after the children during the mother's confinement. She is quite upset because the electric company has just discontinued service because of nonpayment of the bill for the past 8 months.

Memoir of Perce De Long (1880–1961)*

By ALFRED COWAN, M.D.

DR. PERCE DE LONG, the son of Philip and Katherine Gehris De Long, was born on November 11, 1880, at Topton, Berks County, Pennsylvania. He died in Philadelphia on March 12, 1961, of coronary thrombosis.

Perce De Long attended public schools and Franklin and Marshall College. He was graduated from the University of Pennsylvania Medical School in 1907, and interned at the Germantown Hospital. After several years of general medical practice in Scranton, Pennsylvania, he returned to Philadelphia and specialized in neurology. On February 28, 1912, he married Florence Loose, of Hamburg, Pennsylvania. They had two sons, Dr. Philip Loose De Long, presently practicing general medicine in Line-Lexington, Pennsylvania, and Dr. Samuel Loose De Long, an ophthalmologist in Bryn Mawr, Pennsylvania.

Dr. Perce De Long served overseas as a Captain, Army Medical Corps, during World War I. After this interval, in 1919, he specialized in ophthalmology. He has been, at times, on the staff of the Hospital of the University of Pennsylvania, Chief of Ophthalmology of Lankenau Hospital, Chief of the Laboratory of Pathology of the Wills Hospital, and Chief of Ophthalmology of the Philadelphia Municipal Welfare Association.

He taught ophthalmology in the Graduate School of Medicine of the University of Pennsylvania; was made Professor of Ocular Pathology July 1, 1941, and Emeritus Professor of Ophthalmology, July 1, 1953. He was elected a Fellow of the College of Physicians of Philadelphia in 1923 and served as Chairman of the Section on Ophthalmology during 1948–1950. He was not a prolific writer, but did write several important articles. He probably was the first ophthalmologist to report on the use of the electron microscope in eye research (Transactions American Ophthalmological Society, *29:* 335–343, 1941).

Doctor De Long was a natural-born athlete. He played professional baseball before entering medical school—second base on the Cincinnati National League team; he was an outstanding golfer of the Philadelphia area and an excellent swimmer. Besides numerous medical societies he was a member of the Merion Cricket Club, the Merion Golf Club, and the Pine Valley Golf Club. He had the knack of being proficient in nearly everything he tried. He was an expert at playing bridge. A few years ago he took up painting and showed a remarkable talent. Recently he taught himself to play the organ and did very well at it. He was also a good horticulturist.

Perce De Long was always good company—he loved many things in life, but mostly people.

* Read before the College of Physicians of Philadelphia, 6 December 1961. Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

Memoir of John Hinchman Stokes (1885–1961)*

By DONALD M. PILLSBURY, M.D.

DR. JOHN HINCHMAN STOKES died on February 23, 1961, age 75, after a long disabling illness. Thus ended the brilliant career of one of the true giants of dermatology and syphilology. Indeed, Stokes' reputation and accomplishments in syphilology were so towering that his passing might be said to mark the end of a significant era in this specialty of medicine. The like of Stokes and his chief colleagues in the battle against early and late syphilis in all probability will not be seen again.

The writing of a few words of appreciation of John H. Stokes is not an easy task. His was a complex personality, not readily understood. His passion for truth and accuracy was such that he would regard anything other than a balanced word portrait of him as insincere mockery. Stokes was essentially lonely, not gregarious, and admitted few to close friendship. He was possessed of a fierce loyalty to co-workers and colleagues whom he respected. He was guided and controlled by a desire to reach a lofty goal in science and medicine, set early in life, and extraneous influences could not long swerve him from his path. His creed is best expressed in a quotation from the writings of the French mathematician and physicist, Jean Baptiste Biot (1774–1862), which he lettered and illuminated himself, and which long hung over his desk.

> "Perhaps your name, your existence will be unknown to the crowd. But you will be known, esteemed, sought after by a small number of eminent men scattered over the face of the earth, your rivals, your peers in the intellectual Senate of minds; they alone have the right to appreciate you and to assign to you your rank, a well-merited rank, which no princely will, no popular caprice can give or take away; and which will remain yours as long as you remain faithful to Science, which bestows it upon you."

John H. Stokes graduated from the University of Michigan, A. B., 1908, M.D., 1912. His scholastic attainments were attested by his election to Phi Beta Kappa, Sigma Xi, and Alpha Omega Alpha. He was much influenced by the bacteriologist, Frederick G. Novy, particularly by his studies on spirochetes, and hoped to follow a career in basic science. However, the opportunities for such careers at that time were limited, especially for one with family responsibilities. In 1913 he became the first Resident in Dermatology and Syphilology at the University of Michigan. His Chief was Dr. Udo J. Wile, though there was little difference in their ages. Stokes went briefly to the University of Illinois in 1915, and in 1916 accepted the post of Chief of the Section of Dermatology of the Mayo Clinic, then burgeoning to its preeminent status in world medicine and surgery. There can be no question that Stokes contributed significantly to the growth and reputation of "The Clinic" in those days.

The demonstration of *Treponema pallidum*, the development of serologic tests for syphilis, and the synthesis of arsphenamine and its analogues gave a unique clinical opportunity to the era. Stokes seized upon these advances avidly. He was profoundly shocked by what he encountered in patients in whom opportunities for the recognition and adequate treatment of syphilis had been missed. A continuing stream of papers flowed from his pen. He overlooked no opportunity to address local and national medical groups in the furtherance of his dedicated campaign against syphilis. To hear Stokes give a medical address with full fervor was an unforgettable experience. His timing, aptness of phrase, and richness of

* Read before the College of Physicians of Philadelphia, 7 February 1962. Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

metaphor were remarkable. He was a true evangelist, and it is unfortunate that no sound recordings of his addresses are available. Almost single-handed he transformed syphilology from a somewhat disreputable and unpopular specialty to one of increasing stature.

In 1924, Stokes accepted an invitation to become the Chairman and Professor of the Department of Cutaneous Medicine at the University of Pennsylvania. In part this decision was based upon an insupportable sadness over the death of his youngest son Frederick. He dedicated the first edition of *Modern Clinical Syphilology*, as follows:

> "The writing of this book, interrupted by the death of my younger son, Frederick Stokes, October 24, 1923, has been completed in the face of great difficulties. To him, and to my older son, John, it is now dedicated; a symbol of the belief that we still carry on together, though one is gone; and a memorial to the boy Frederick's ardent and fearless spirit."

The older son, John, was killed on D-Day, 1944, during the invasion of Europe by the Allied Forces. These were two of several personal tragedies which were to be Stokes' lot. One had the feeling that, despite external appearances, he never recovered completely from these hammer blows of Fate.

The appearance of the first edition of *Modern Clinical Syphilology* was a medical publishing milestone of first importance. The second and third editions were published in 1934 and 1944, respectively. While the first edition was less encyclopedic than the later ones, it was probably the best and most influential, because it was intensely personal, and exerted a major influence on the course of an important branch of medicine. In its highly original method of exposition it was a welcome departure from the stodgy medical textbook styles of the day, and the thoughts expressed in it still leap from the pages with clarity and vigor.

Stokes wrote four other books, *The Third Great Plague*, *Today's World Problem in Disease Prevention* (both for lay readers), *Dermatology and Syphilology for Nurses* (four editions), and *Fundamentals of Medical Dermatology*. He wrote approximately 250 medical articles, covering a wide range of dermatology, syphilology and psychosomatic medicine. His work in the last field was possibly less fruitful than in the others. During this period Stokes became a devotee of what he termed "bibliocresis". This was essentially a weaving together of numerous dissociated items from the medical literature with his own theories and personal experiences. The resultant reports, though written with brilliance and conviction, did not always withstand close scientific scrutiny and practical application.

Stokes was one of the original members of the Cooperative Clinical Group, founded by O'Leary (Mayo Clinic), with Moore (Johns Hopkins), Cole (Western Reserve), and Wile (Michigan). This furnished the basis for modern cooperative studies in syphilis and many other diseases. It provided a starting point for the great expansion of Venereal Disease Control by the U. S. Public Health Service, under the vigorous direction of Dr. Thomas Parran (later Surgeon General). Almost all of the more prominent officers of the Public Health Service and National Institutes of Health during the past fifteen years participated in this effort to some degree in their early careers, and many of them have spoken to us of the tremendous influence which Stokes exerted upon them.

With the clouds of war gathering, it became evident that increased emphasis upon venereal diseases was necessary to the national health effort. The Sub-Committee on Venereal Diseases of the National Research Council was given much increased support and authority. Joseph Earle Moore was Chairman, and Stokes was a principal member and chief protagonist. Each regarded himself as a balance wheel for the other. Sparks of great brilliance flew in word and writing, but the spirit of mutual respect and regard between these two extraordinary men never wavered. It was a privilege to be a friend and colleague of both, and to

hear tales of one or the other almost without end.

These appreciations would be incomplete without some notes of Stokes, the teacher of medical students and residents. At the University of Pennsylvania Hospital he appeared officially once weekly, on Thursdays from 8:30 a.m. to 2:00 p.m., first with medical students and then with the residents. Two hours of lecture, quizzing and case demonstration were spent with the Junior Class, and, unlike most medical students, they came in complete force, in sickness or in health, in fair weather and foul. The reading assignments were prodigious, and the class requirements rigid. No student in Stokes' class failed to learn a great deal, and none of them has ever forgotten the experience, because he had served under an outstanding but unrelenting taskmaster. Nor did any resident approach a task under Stokes' direction with anything less than the most meticulous preparation and attention. With the flick of a phrase Stokes could unmask the pretender to knowledge, kindly but effectively. There were some who preferred not to express disagreement with some idea of Stokes, but theirs was the loss in missing the opportunity to cross intellectual swords with a master dueler.

At the end of World War II, Stokes resigned as Chairman of the Department of Cutaneous Medicine at the University of Pennsylvania, after serving twenty-one years in this capacity. He had organized The Institute for the Study of Venereal Diseases under University auspices, for studying these diseases from all standpoints—investigative, clinical, religious, legal, ethical, psychological, and sociological. The Institute flourished for a few years, but financial support became increasingly uncertain, and Stokes was unable to give it vigorous direction by reason of steadily failing health. All of this was a source of unspeakable frustration and disappointment to him; the disease to which he had devoted the major portion of his professional life was fading from the medical scene, and a once phenomenally energetic body could no longer meet the demands of an active and restless mind. This was a source of great sorrow and sympathy to all his colleagues, and we prefer to remember the man who was such a remarkable figure of strength and energy, rather than the declining figure of the past decade.

Stokes received many honors. He was one of the small group of founders of the Society for Investigative Dermatology, and an early President. He was President of the American Dermatological Association. He was a member of the Commission of Experts on Syphilis of the League of Nations, a Special Consultant to the U. S. Public Health Service, a Senior Surgeon (Res.), U. S. P. H., a Civilian Consultant to the Secretary of War, among many similar appointments. His awards included the Meritorious Service Medal, State of Pennsylvania, 1938, Citation Third Service Command, U. S. Army, 1945, Citation War Department 1945, Citation Army and Navy 1947, and the William Freeman Snow Award for Distinguished Service to Humanity 1946. He was a Corresponding Member of the Vienna, Argentine, British, French, Netherlands, Austrian, and Danish Dermatological Societies. Special issues of the *Journal of Investigative Dermatology* (December, 1946) and of the *American Journal of Syphilis* (March, 1947) were published in his honor.

John H. Stokes was married in 1908 to Della Bixler Lee, and there were two sons by this marriage, both now dead. In 1925 he married Margaret Ann Maris who died with an infant daughter Johanne in 1932. In 1933 he married Eleanor Heaps McGahey, who survives him along with three children, Tawn Janice, Eleanor Anne, and James William. His son is a first year medical student at the University of Pennsylvania.

To do justice to the personality and career of Dr. John H. Stokes in a few pages is impossible. His activities and accomplishments during a professional life of over forty years would require a large volume to record, and

even this could hardly catch all the facets of a remarkable personality. Here was a man from an uncommon mold, constantly striking out with vigor, fearlessness, and utmost candor, at the risk of incurring enmity from some, for what he considered best and right in medicine and life. There is much evidence that the world of medicine is better because "JHS" passed among us.

Acknowledgment: The collaboration of Dr. Herman Beerman in preparing this *Memoir* is acknowledged.

Memoir of James Poland Lewis (1901–1961)*

By GEORGE M. LAWS, M.D.

JAMES Poland Lewis was born in Kingston, Pennsylvania, on February 17, 1901. He was educated at the Wyoming Seminary and the University of Pennsylvania, where he took a two year premedical course and graduated from the School of Medicine in 1924. He had two years of internship at the Presbyterian Hospital before entering the general practice of medicine in Philadelphia.

In 1930 he limited his practice to obstetrics and gynecology. He was on the staff of the Presbyterian and Philadelphia General Hospitals, where at both hospitals he later became Chief of Obstetrics and Gynecology, and kept active in this specialty for the rest of his life. He was also an Associate in Obstetrics and Gynecology in the University of Pennsylvania School of Medicine and Graduate School of Medicine.

He became a Fellow of the College of Physicians of Philadelphia in 1938. He was also a Fellow of the American College of Surgeons, a Diplomate of the American Board of Obstetrics and Gynecology, and a Member of the American Association of Obstetricians and Gynecologists, the Philadelphia County Medical Society, and the American Medical Association. He was a Past President of the Obstetrical Society of Philadelpnhia, the Presbyterian Hospital Medical Staff, and the West Philadelphia Medical Association. He had been a Consultant to the South Eastern Dispensary, Chief of the Maternity Hospital, and Assistant to the Philadelphia Lying-In Hospital.

Dr. Lewis served on active duty with the United States Navy from 1943 to 1946. He was a Lieutenant Commander, and later Commander, Medical Corps, U.S.N.R. Part of his military service was at the Naval Hospital at Norfolk, Virginia, where he was Chief of Obstetrics and Gynecology. He also served in the Pacific Theatre of Operations. After the war, he became Civilian Consultant in Obstetrics and Gynecology at the U. S. Naval Hospital in Philadelphia.

Dr. Lewis had the qualities of mind and heart that make a good doctor and professional attainments that made him exceptionally skillful in his specialty. He was one of those talented individuals who can do many things well. He was an accomplished musician, an athlete, an amateur magician, a radio operator, and a student of modern science. His personality is portrayed in a Resolution by the Board of Trustees of the Presbyterian Hospital which stated that, "he endeared himself to every patient, doctor, nurse, employee, and volunteer worker in this hospital who knew him, as colleague, counsellor, and friend, as well as devoted husband and father."

He died of coronary thrombosis on October 24th, 1961. His many friends have contributed generously to the Presbyterian Hospital in honor of his memory. Surviving are his wife, the former Marion Butts; two sons, James P., Jr., and Dr. John D. Lewis; two daughters, Mrs. Marion Lewis Congdon and Miss Anne Louise Lewis; a sister, Mrs. Anne Van Vliet, and five grandchildren.

* Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

Memoir of John Carnett Howell (1901–1961)*

By TRUMAN G. SCHNABEL, M.D.

AFTER having had a full day of it in surgery as well as an emergency consultation at midnight on the same day, John Carnett Howell, one-time Fellow and for the last years of his life a non-resident Fellow of the College, died suddenly in Tyrone, Pennsylvania, early on the following morning of June 10, 1961.

He was born in nearby Altoona on April 11, 1901, the son of a surgeon who had been an oarsman in the University of Pennsylvania eight-oared shells of 1896–1898. Rowing in the same shell was John Berton Carnett, who later became a Fellow of the College, an able teacher, a dedicated and greatly admired surgeon. Clearly then, Howell was named for this classmate and close friend of his father, Dr. William Henry Howell. His father was chiefly of Welsh extraction, while his mother, Frances Regina Kempf, was of German-French origin. The son, 'Jack', reflected many of the sterling qualities of his namesake. This is not surprising for he saw Doctor Carnett on visits during his years at school, in college, while studying medicine, as an interne, and in years of association with him as an inspiring and stimulating chief.

Jack graduated from the Atlantic City High School after preliminary schooling at Altoona. Of fine physique, he was athletically inclined and, as might have been predicted, preferred rowing. It was not, however, until he was taking premedical training in the College Department of the University of Pennsylvania that he, like his father and Dr. Carnett, pulled an oar on the varsity shell for two years. He received his medical degree from Penn in 1924. For years thereafter, Dr. Howell contributed to Varsity Club projects in rowing, feeling that rowing is the finest of sports and that sportsmanship of the best sort, fostered by athletics, carries over into personal character. For a time he belonged to the Undine Barge Club on the Schuykill River. When Jack was laid to rest, he wore the Varsity Club button in his coat lapel.

His undergraduate fraternity was Sigma Alpha Epsilon, and his medical one, Nu Sigma Nu. Early interest in surgery was manifested by membership in the D. Hayes Agnew Surgical Society, over which he presided during his last year in medical school. Surgery continued to be his special interest for the rest of his life, twenty-nine years in Philadelphia and the last six years in Tyrone, Pennsylvania.

After graduation from medical school he interned at the Presbyterian Hospital and soon thereafter was associated for a time in office practice with Dr. William Bates. In due time, he served on the visiting surgical staffs of the Philadelphia General, Graduate, Presbyterian, and Nazareth Hospitals. In Tyrone, Howell was Chief Staff Surgeon of its hospital, and functioned as such to the great satisfaction of the entire community, both lay and professional.

Besides being a capable surgeon and physician, he was highly regarded as a teacher. He eventually became a Professor of Surgery at the Graduate School of Medicine at the University of Pennsylvania; teaching for the most part at the Graduate and Philadelphia General Hospitals, where students found him thorough and practical in approach. Generous and untiring in his efforts to help students "get a break", his enthusiasm for their good qualities was never dimmed by self-interest. As evidence of his torch-bearing potential, his professional colleagues in Tyrone gained much by their contact with him.

Inspection of operating room schedules and examination of our late Fellow's bibliography make it apparent that he was chiefly a general

* Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

surgeon with a predilection for the managment of patients with malignancies. This interest developed out of his activity in the Radiological Division at the Philadelphia General Hospital, to which all patients were assigned when afflicted with malignant disease. It was in this department of the hospital that he worked as an associate surgeon to 1927, as a visiting surgeon to 1934, and as a consulting surgeon to 1957. On May 2, 1957, he was awarded honorary membership in the Blockley Radiological Society, "in recognition of many years of devoted service as a distinguished Surgeon, Teacher, Scholar, Scientist and Author." He is the only non-roentgenologist to have received this citation.

With a rich background of experience gained at Blockley, Dr. Howell worked diligently in the cause of the American Cancer Society, both in Philadelphia and in Blair County. He served on divisional boards and was a member of executive medical and scientific committees. While director of our local cancer board, he took an active role in the Society's public education program. He was unselfish with his time and spoke on numerous occasions to various groups in industries, churches and schools. In fact, Howell helped to pioneer the Cancer Educational Program in business and industry, the first such effort in this country. He brought to cancer problems his valuable experience in industrial medicine attained by long-time conduct of Graduate Hospital's Industrial Clinic and as a consulting surgeon to the Philadelphia Electric Company, Baltimore and Ohio Railroad, and the Pennsylvania Railroad.

He belonged to leading medical organizations: Diplomate of the American Board of Surgery; Fellow of the American College of Surgeons; member of the Philadelphia Academy of Surgery; Fellow of the College of Physicians of Philadelphia; member of the Blair County Medical Society, the Pennsylvania Medical Society, and the American Medical Association. He served actively on county society committees related to breast cancer, appendicitis mortality, industrial medicine and civil defense, and also belonged to the Philadelphia Nursing Council.

As avocations, he was a member of the Philadelphia Welsh Society and enjoyed attending its Eisteddfod Music Festivals. He was fond of group singing, had a fine baritone voice, and enjoyed choral music and concerts.

Quietly and deeply religious, he served on church councils of the Church of the Holy Communion in Philadelphia for about eight years, and on the Council of the First Lutheran Church in Tyrone for two and one half years. He was a Thirty-Second Degree Mason.

On his death, his family received Resolutions from the Blair County Medical Society, Blair Division of the American Cancer Society, Tyrone Hospital Staff, Board and Auxiliary, and the Tyrone Civil Defense Group. These tributes testified to Howell's deep concern for people, always unselfishly dedicated to serve beyond the "call of duty". The community of Tyrone stood still in commemoration on the morning of his funeral. His patients felt helpless at the prospect of carrying on without him.

On one occasion, Dr. Howell filled out a reunion form for his medical classmate, Dr. Samuel X Radbill. Under "hobbies", he wrote, *Living*. That was John Carnett Howell. He really lived . . . and will always live in the hearts of his friends, professional and otherwise, his patients, and above all, his dear wife and children.

Memoir of Robert A. Matthews (1903–1961)*

By KENNETH E. APPEL, M.D.

TO write a memorial of a friend is a privilege. When there is so much that is positive which can be said, the sadness is in a measure counterbalanced. A memorial is the public recognition of the passing of a prominent person. It presents the significant chronology of his life: important achievements are indicated; prominent characteristics of the personality are sketched in appropriate perspectives and accents. A tribute of his colleagues is recorded publicly.

Dr. Robert A. Matthews, Professor of Psychiatry and Head of the Department, Jefferson Medical College, met his death in an automobile accident on the Black Horse Pike near Williamstown, New Jersey, on June 23, 1961. There was a head-on collision at 5:00 p.m. because the driver of the other car apparently had fallen asleep in his automobile.

Dr. Matthews was fifty-eight years of age. He was born in Johnstown, Pennsylvania, on March 31, 1903. The Pennsylvania State University awarded him a B.S. degree in 1925. He was graduated from the Jefferson Medical College of Philadelphia in 1928.

After a two year internship at the Philadelphia General Hospital, he became Chief Resident Physician of the Philadelphia Hospital for Mental Diseases (now the Philadelphia State Hospital), and subsequently served four years as Clinical Director of that institution. At the same time, he served as Physician-in-Charge of the Philadelphia Institution for the Feeble-Minded.

Dr. Matthews began his teaching career at Jefferson in 1930, and from 1946 to 1949 was Acting Head of the Department of Psychiatry, while Dr. Baldwin Keyes was away in the military service. From 1942 to 1946, Dr. Matthews was Instructor in the Neuropsychiatric Indoctrination Program for U. S. Naval Medical Officers. He was Professor and Head of the Department of Psychiatry, Jefferson Medical College, from July 1958, on Dr. Keyes retirement, to the date of his death.

In 1949, Dr. Matthews went to the Louisiana State University School of Medicine in New Orleans, and in 1950 became Professor of Psychiatry and Head of the Department of Psychiatry and Neurology at that University. He served in this position from 1950 to 1956.

In 1956, Dr. Matthews was appointed Deputy Secretary of Welfare and Commissioner of Mental Health for the Commonwealth of Pennsylvania. In this position he accomplished a great deal toward the establishment of progressive programs in State Mental Hospitals. He gave much emphasis to the care of emotionally disturbed and mentally retarded children, encouraged the establishment of psychiatric wards in general hospitals and the development of out-patient clinics throughout the state. He was Consultant to the Office of the Surgeon General, U.S. Army, from 1953 until his death.

Dr. Matthews served as a Rockefeller Fellow in Psychiatry at the Institute of the Pennsylvania Hospital in Philadelphia from 1935 to 1936. He was certified a diplomate of the American Board of Psychiatry and Neurology in 1937.

Intensely interested in psychiatric education, Dr. Matthews instituted a series of psychiatric seminars, as part of Jefferson's joint program of graduate studies with The Pennsylvania State University. He was an able teacher and administered the affairs of his department with vision and wisdom. He was admired and loved by those who worked with him and deeply respected by his students.

* Read before the College of Physicians of Philadelphia, 6 December 1961. Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

His high rank was evidenced by many positions and honors. He had been President of the Philadelphia Psychiatric Society and of the Pennsylvania Psychiatric Society. He was Chairman of the American Psychiatric Association Committee in liaison with the American Academy of General Practice. He was a Fellow of the American College of Physicians, American Psychiatric Association, American Medical Association, American Association of Mental Deficiency, College of Physicians of Philadelphia, and a member of the Pennsylvania Medical Society, Philadelphia County Medical Society, Philadelphia Neurological Society, Southern Psychiatric Society, and the New Orleans Society for Neurology and Psychiatry.

Dr. Matthews' hospital appointments were many. Among these were positions as Consulting Psychiatrist, DePaul Sanatorium, New Orleans; Psychiatric Consultant, VA Hospital in Nevada; Consultant in Neuropsychiatry, VA Hospital, Coatesville, Pennsylvania; Chief, Department of Neuropsychiatry, Delaware County Hospital; Chief Neuropsychiatrist, Nazareth Hospital, Philadelphia; Active Consulting Psychiatrist, and Attending Psychiatrist, Philadelphia General Hospital; and Psychiatrist to the Institute of the Pennsylvania Hospital in Philadelphia.

The breadth of Dr. Matthews' interests and activities are shown by the titles of some of his recent publications. 'Fact and Theory in Psychosomatic Medicine', 'How to Recognize and Handle Abnormal People', 'The Application of a Therapeutic Community Principle to a State Mental Health Program', 'Psychiatric Emergencies in General Practice', 'Resistances Encountered in Teaching Psychiatry', 'The General Practitioner and the Aging Patient', 'Factors in the Success of a Public Mental Health Program', 'Psychiatry and the General Practitioner', 'The Psychiatric Unit in a General Hospital'.

Dr. Matthews lived in Penn Valley with his wife, the former Mary Paxson, and four of his five daughters, Barbara, Sandra, Anne, and Jean. The fifth daughter, Mrs. William T. Coghlan, wife of a surgeon, lives in Beaver Falls, Pennsylvania.

It was my grieving honor to read the following Memorial to Robert A. Matthews at his Funeral Service on June 27, 1961, at Philadelphia:

Custom as well as spontaneous impulse and feeling bring us here today. Friends, relatives, family have gathered here. It is a Meeting, as so often gathered in Philadelphia, without ceremony and ritual, where the Society of Friends has been accustomed to bring people together informally on the basis of community of feeling and dedication. This is a coming together to indicate by our presence many things. There are many happy memories: The sparkle and alertness of the eyes, showing the keeness, the awareness of things obvious, and often deeper implications than were first apparent. There was the not infrequent turning of his head and glance and attention to make sure those present were with him—that they knew, and he knew, what it was all about. There was a kind of social inclusiveness—his lines of sight with their comprehensive shifting and searching. There was kindness, warmth and gaiety in his appearance,—from the eyes to the face, to the voice— with its expression of words, phrases, and opinions. His observations and conclusions came readily, but not impulsively, and casually. They were restrained and kindly but had cogent, deep and forceful implications.

His pace and gait were lively but not driven. His greetings were friendly, whether the occasion was of serious business or of festivity. He had his repertories whether of humorous stories and incidents, or of "telling" experiences which drove home a point. He had humor, which brought fun and balance to many occasions:—whether his attempts to trim his hair short as a crew cut—when there was not so much to clip—or his jolly little cap—or his white coat and black tie for formal occasions. He mixed the psychological and the biological in balanced proportions in

psychiatry. In his person and in his views the psychic and the somatic were wholesomely represented.

And some of my memories run to Christmas Eve when, in Pickwickian attire and pixie mood, with solid friendliness and pride, he brought his lovely wife and jolly children, full of spirit and enthusiasm. They all came to carol and drink a communion of friendship and neighborliness in the warmth of mulled wine.

Other memories also come of him: Doing a job and learning psychiatry—in far off, at that time, isolated, indifferent—I was going to say almost zoological—Byberry. Or learning the refinements of psychiatry with Drs. Bond and Strecker in the comforts of the Pennsylvania Hospital. Or in gay New Orleans, where the distractions of Royal and Bourbon Streets, the delicious delicacies, exotic drinks, and jouncing jazz—did not too much divert him from the serious business of improving psychiatric care at the Charité. And as Chairman of the Department at Louisiana State University he continually strove to improve the quality of psychiatric education in medical schools. The community and the state hospitals also felt his influence—he brought Dr. Maxwell Jones from England for vital conferences in the state hospitals. He had fruitful collaboration with his colleague at Tulane—Bob Heath—who was exploring both the neurological and chemical aspects of schizophrenia, and modifying psychoanalysis.

His calmness, friendliness, resourcefulness, was shown when he was taking me from Biloxi to New Orleans to place me on a plane. He ran out of gas 100 miles from nowhere. I was wild—mildly turbulent as they say of a plane in rough, uncertain going—but I tried to contain myself. Then came his quiet reassurance that I should not worry and that we would arrive on time. Shortly a humble Cajun family in a doubtfully performing auto were pushing us 30 miles to a gas station. They refused any compensation, though obviously in need of it with their huge family of children—so persuasive, so intriguing, was Bob Matthews' appeal.

In Charleston, again helping psychiatric education with his practical discussions on Emergencies in General Practice, or—The Importance of Giving Psychiatric Information to the Police Force—giving them an elementary understanding of acute emergencies, the intransigencies and aberrancies of human conduct and how to handle them.

There in a day of delightful Spring weather, surrounded with Southern hospitality, he seemed receptive to tackling the Commissionership of Mental Health of Pennsylvania. With the driving, determined, dedicated Harry Shapiro and the enlightened, sympathetic, supportive Governor Leader, he introduced a new era in care of the mentally ill in Pennsylvania. It was in his regime that the Western State Psychiatric Hospital with Dr. Brosin burgeoned into one of the great centers of psychiatry in the country—when the Eastern Pennsylvania Psychiatric Institute, with the persistent and resourceful Dr. John Davis, got off the ground and was realizing a dream of new development of psychiatry in Philadelphia—where public psychiatry could offer not only the best in modern methods of treatment, but also could develop a phalanx of basic research, rising to refinements and penetrations that are represented by the best in the world. The state hospitals themselves felt this new influence, for development and progress, in their functions.

And finally, in a historic professorship at the great medical school at Jefferson—where Dercum, Strecker and Keyes had been his predecessors, he showed leadership in developing psychiatry. He organized a large, successful, aggressive section of psychiatry in the great Jefferson Hospital. He established this new section with marked success—an undertaking that has been difficult to achieve in Philadelphia Medical Schools. With all this—teaching, explorations of new types of service, private practice, he did not abandon his efforts in behalf of public psychiatry—to improve

the treatment of those who could not afford the best.

One of my last meetings with him was on the Medical Board at the Eastern Pennsylvania Psychiatric Institute where we were searching for new methods and procedures in organization and practice. He contributed more than his share of resourceful suggestions to strengthen the foundations of that new institution—forging new precedents and instruments of research into a public hospital.

His home and family were a delight to enter. There is a presence here we commemorate. It will always be in our hearts and its influence in our minds and decisions.

As we commemorate, we dedicate our energies anew to the great and the constructive—taking with us his homely, humorous and balanced views of the ideal and the practical—dedications and directions for which Bob Matthews stood and lived. Our love goes to his family and relatives. When separations come, such as this, I always think of the great religious leaders of the world—but also of Socrates, Gandhi, Father Damien, Pasteur, Schweitzer—lives dedicated to the improvement of the lot of their fellow men. Plato concludes of Socrates: "such was the end of our friend." He was called wise, just and great. Bob Matthews will remain with us as friend, builder and co-laborer in the best of this great tradition. And from Avon come echoes, consoling, warming, energizing—as Bob Matthews would have liked:

"When to the sessions of sweet silent thought
I summon up remembrance of things past,
I sigh the lack of many a thing I sought,
And with old woes new wail my dear time's waste:
Then can I drown an eye, unus'd to flow,
For previous friends hid in death's dateless night,
And weep afresh love's long since cancell'd woe,
And moan the expense of many a vanish'd sight:
Then can I grieve at grievances foregone,
And heavily from woe to woe tell o'er
The sad account of fore-bemoaned moan,
Which I now pay as if not paid before.
But if the while I think on thee, dear friend,
All losses are restor'd and sorrows end."*

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* *The Sonnets: The Tudor Shakespeare*, edited by Raymond M. Allen, The Macmillan Company, New York, 1913.

Memoir of Robert P. Glover (1913–1961)*

By J. RODERICK KITCHELL, M.D.

ROBERT P. Glover, a Fellow of the College since 1954, was born in Nyack, New York, July 12, 1913. He died at his home in Cynwyd, Pennsylvania, February 1, 1961.

He received his Bachelor of Science degree from Wheaton College in 1935 and his degree of Doctor of Medicine from the University of Pennsylvania in 1939. Intern years were spent in Germantown Hospital from 1939 to 1941 and he was in residence in general surgical and thoracic surgical work at the Mayo Clinic at Rochester, Minnesota, from 1941 to 1946. Post-graduate work at the University of Minnesota in 1946 won him the degree of Master of Science in Surgery.

A Diplomate of the American Board of Surgery in 1949 and of the American Board of Thoracic Surgery in 1950, his practice was limited to thoracic and cardiovascular surgery in the spring of 1947.

He was Assistant Clinical Professor of Surgery at the University of Pennsylvania School of Medicine and Chief of the Department of Thoracic and Cardiovascular Surgery at Presbyterian, St. Christopher's, and Fitzgerald Mercy Hospitals. He was co-chief of the Department of Thoracic Surgery at Episcopal Hospital. He was also on the staff of the Coatesville Veterans Administration Hospital, Good Samaritan Hospital in Pottsville, U. S. Army Hospital at Valley Forge, Lankenau Hospital in Philadelphia, and Germantown Hospital.

In addition to being a member of the American Medical Association and medical societies of Pennsylvania and Philadelphia County, he was a Fellow of the American College of Surgeons. He was active in the early days of the American College of Cardiology, serving as its President in 1953 and 1954. It was largely due to his efforts that this college assumed its present stature. In all he belonged to 28 professional medical groups, some of them abroad. He was also a member of the Penn Club and the Union League of Philadelphia.

During all his professional life, Dr. Glover had a great interest in research. He was an internationally-known authority on cardiovascular surgery, especially the correction of damaged heart valves. He was the author of sections on this subject in several textbooks and was editor of a recent book, "Practical Diagnosis of Surgical Heart Disease." His latest book on mitral valvular surgery is soon to be published. He also produced a total of 85 technical articles for medical journals. Many of these were written with his associates, although most of the composition was done by Dr. Glover. On two occasions he and his associates won the Billings Gold Medal of the American Medical Association for the best exhibit at annual conventions.

In 1953 he established the Cardiovascular Research Laboratory at Presbyterian Hospital and directed the surgical heart research program there for the last seven years. His efforts were largely responsible for the recent completion of plans and the start of construction of a new million dollar medical science research laboratory at Presbyterian Hospital.

Although Bob Glover was an outstanding scientist, perhaps his greatest gift was his talent as an artist in medicine. He was a teacher in the full sense of the word. His talks, to either professional or lay audiences, were interesting and understandable—models of simplicity and directness. His ability to sit down with either the patient or the referring physician and explain to them satisfactorily the

* Read before the College of Physicians of Philadelphia, 1 November 1961. Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

diagnosis and need for therapy of a given type was unparalleled in my experience. He was able to impart a sense of hope to the patient even though there may have been little hope. In other words, he was a doctor who was able and willing to really take care of sick people. He will be missed not only by the members of his family and this College but also by the many referring physicians who depended on him for advice and help and especially by all the patients whose lives were made happier through his skill.

Report of the Secretary for the Year Ended December 19, 1961

Stated Scientific Meetings

		Attendance
January	Forty-fifth Nathan Lewis Hatfield Lecture—Peter N. Witt, M.D.	48
February	Eighty-first Mary Scott Newbold Lecture—Ralph W. Brauer, Ph.D.	110
March	Eighty-second Mary Scott Newbold Lecture—Wallace P. Rowe, M.D.	70
April	Fortieth James M. Anders Lecture—Victor A. McKusick, M.D.	70
May	At the Philadelphia County Medical Society—Presentation of the Strittmatter Award to William N. Parkinson, M.D., by Charles M. Thompson, M.D., Chairman, Award Committee. Presentation of the Benjamin Rush Awards to Mr. Bruce D. Smith and to Mrs. Arlene Dickler Grass, by David A. Cooper, M.D., Chairman, Benjamin Rush Award Committee. Presentation of citations to physicians who have completed fifty years in the practice of medicine, by Thomas W. McCreary, M.D., President, Medical Society of Pennsylvania.	250
October	Twenty-first Alvarenga Prize Lecture—Seymour S. Kety, M.D.	250
November	Joint Meeting with the Philadelphia County Medical Society. The Forty-first James M. Anders Lecture—David D. Rutstein, M.D.	60
December	Seventy-fourth Thomas Dent Mütter Lecture—Colonel Joe M. Blumberg, M.C., U.S.A.	95

Regular Business Meetings

	Total Ballot
January 4, 1961	303
February 1, 1961	290
March 1, 1961	281
May 10, 1961	378
October 4, 1961	344
December 6, 1961	279

The College of Physicians of Philadelphia awarded the Alvarenga Prize Award on July 14, 1961 to Seymour S. Kety, M.D., for his outstanding work on cerebral blood flow and the effect of drugs on the central nervous system.

Sections of the College:

	Membership
Ophthalmology	73
Otolaryngology	54 & 2 Honorary
General Medicine	150
Public Health, Preventive and Industrial Medicine	63
Medical History	78

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MEMBERSHIP

	Fellow	Non-Res.	Assoc.	Honorary Foreign	Honorary U.S.	Hon. Assoc.	Total
December 27, 1960	1045	144	0	2	5	2	1198
Died during year	17	7			1		25
Resigned	3	3					6
Elected	48	2					50
Transferred from Resident to Non-Resident		8					8
Transferred from Non-Resident to Resident	1						1
Forfeited	2						2
December 19, 1961	1064	145	0	2	4	2	1215
Life Membership							
New Type							
Under 70	26	6					
Over 70	20	8					
Old Type (Commutation of dues)	7						
	53	14					
Dues Remitted:							
Before 1961	33	7					
During 1961	6						
	39	7					
Annual Contributors as of December 19, 1961	972	122					

THOMAS E. MACHELLA, M.D.
Secretary

Report of the Treasurer for the Year Ended November 10, 1961

Assets

General Fund:		
Cash in bank and on hand		$23,607.04
Maintenance and Reserve Fund:		
Cash in bank	$731.39	
Investments	8,358.23	
		9,089.62
Miscellaneous Contributions Fund:		
Cash in bank		350.00
Library Historical Collections Fund:		
Cash in bank		1,918.18
Special Contributions for use of the Library:		
Cash in bank		12,545.25
Trust Funds:		
Uninvested principal cash	38,519.37	
Uninvested income cash (restricted)	4,190.71	
Mortgage	38,250.00	
Real estate	158,905.33	
Bonds	333,090.90	
Preferred stocks	276,268.79	
Common stocks	377,576.49	
		1,226,801.59
Plant Fund:		
Land—15-25 South 22nd Street	95,000.00	
Building	1,420,747.93	
Furniture and fixtures	1.00	
Deposits on perpetual fire insurance policies	11,462.28	
		1,527,211.21
		$2,801,522.89

Funds

General Fund:		
Library general account		$9,968.00
Library medical documentation service		8,005.22
Life membership—uninvested funds		246.00
Reserve for contingencies—uninvested funds		190.02
Unexpended operating fund balances		
Current operations	$2,172.90	

Publication committee	1,248.78		
President's room	525.00		
Friends of library	20.00		
Books	1,017.92		
Rare books	152.96		
Campaign expense	135.95		
Portrait	126.47		
Harvey's "De Motu Cordis" Facsimile	(202.18)	5,197.80	$23,607.04
Maintenance and Reserve Fund—principal			9,089.62
Miscellaneous Contributions Fund—principal			350.00
Library Historical Collections Fund—principal			1,918.18
Special Contributions for Use of the Library—principal			12,545.25
Trust Funds:			
Principal net worth			
Discretionary common trust fund	1,145,288.38		
Legal common trust fund	24,097.94		
Trust funds not pooled	14,974.56		
Fund for purchase of units in discretionary common trust fund	38,250.00	1,222,610.88	
Income net worth			
Discretionary common trust fund	3,140.28		
Legal common trust fund	657.58		
Trust funds not pooled	392.85	4,190.71	1,226,801.59
Plant Fund—principal net worth			1,527,211.21
			$2,801,522.89

NOTES: The various fund investments are shown at their recorded values, which values substantially represent cost.

GENERAL FUND

STATEMENT OF CASH RECEIPTS AND DISBURSEMENTS

November 11, 1960 to November 10, 1961

Receipts:		
Income on investments, net of agent's fees:		
Trust funds	$71,277.91	
Less:		
Amount transferred to income cash of the several restricted trust funds	10,337.29	
Erlanger garage expenses paid	6,019.64	
Amount transferred to principal to reduce value of Erlanger garage investment	3,840.77	
	20,197.70	
	51,080.21	
Add: income transferred from Erlanger garage to Discretionary Fund in excess of profits earned by garage	3,726.91	
		$54,807.12
Income from funds, principal of which is not administered by the College		1,951.80
Interest on mortgage		1,784.54

Interest on U. S. Treasury bills		551.03	
			$59,094.49
Contributions:			
Fellows dues		60,464.00	
Life membership		874.00	
Use of hall and projector		2,755.00	
			64,093.00
Transfers from other funds:			
To cover deficit in current operations for 1959–60:			
Miscellaneous Contributions Fund		3,358.83	
Maintenance and Reserve Fund		1,391.03	
For painting exterior of building			
Maintenance and Reserve Fund		2,290.00	
			7,039.86
Library:			
Contribution plan	19,407.46		
Photostats, fines, etc.	21,412.46	40,819.92	
Medical documentation services		38,292.14	
			79,112.06
Miscellaneous			1,333.25
Total receipts			210,672.66
Disbursements:			
Operating expenses:			
Hall committee		$34,707.35	
Office of the Secretary		7,330.75	
Office of the Treasurer		8,238.05	
Pensions		3,042.32	
Campaign expenses		10.00	
Publication committee		4,792.58	
Books		1,246.36	
Entertainment committee		1,103.08	
College collections committee		3,710.28	
Library			
Salaries	$69,842.03		
Books, journals, supplies, etc.	37,121.11	106,963.14	
Medical documentation			
Salaries	23,487.78		
Other expenses	6,799.14	30,286.92	
General funds used to purchase units in Discretionary Common Trust Fund for Pension Reserve Fund		657.68	
Painting exterior of building		2,290.00	
			204,378.51
Excess of receipts over disbursements			6,294.15
Add: Cash balance, November 10, 1960			17,312.89
Cash balance, November 10, 1961			$23,607.04

ANNUAL SUMMARY STATEMENT

Statement of Cost of Investment Units Purchased in Discretionary Common Trust Fund by the General Endowment Fund

November 12, 1960 to November 11, 1961

Balance, November 12, 1960		$405,349.70
Receipts:		
Entrance contributions	$2,500.00	
Voluntary contributions from fellows, etc.	1,671.42	
Bequest from Estate of John E. Hume	828.17	
Book of Remembrance	285.00	
Amortization of mortgage—13th and Locust Streets	2,250.00	
	7,534.59	
Deduct:		
Amount insufficient to purchase one unit, credited to unit adjustment account	1.97	
		7,532.62
Balance, November 11, 1961		$412,882.32

Statement of Cost of Investment Units Purchased in the Discretionary Common Trust Fund by the College Extension Fund

November 12, 1960 to November 11, 1961

Balance, November 12, 1960		$2,624.96
Receipts:		
Voluntary contributions from Fellows	$222.50	
Income earned on invested principal	122.33	
	344.83	
Less: Amount insufficient to purchase one unit, credited to unit adjustment account	5.82	339.01
Balance, November 11, 1961		$2,963.97

Statement of Cost of Investment Units Purchased in the Various Trust Funds by the Restricted Endowment Funds

November 12, 1960 to November 11, 1961

Discretionary Common Trust Fund

Balance, November 12, 1960		$552,699.75
Receipts:		
S. Weir Mitchell Associates journal fund	$19,623.42	
General endowment for the library	3,780.00	
Life membership fund	705.84	
Pension reserve fund	1,118.82	
Library historical collection fund	5,000.00	
Transfers from unit adjustment account:		
S. Weir Mitchell Associates journal fund	42.38	
General endowment for the library	21.19	
Life membership fund	21.19	
Pension reserve fund	21.19	
Library historical collection fund	21.19	
Transfers from income to principal:		

Robert Abbe custodianship fund	10,000.00	
	40,355.22	
Less: Amounts insufficient to purchase one unit, credited to unit adjustment account	107.53	
		40,247.69
Balance, November 11, 1951		592,947.44
Legal Common Trust Fund		
Balance, November 12, 1960 (no change during year)		23,500.00
Trust Funds not Pooled		
Balance, November 12, 1960	14,941.06	
Profit on sale of securities (William Zentmayer Fund)	33.50	
Balance, November 11, 1961		14,974.56
Total restricted endowment funds, November 11, 1961		$631,422.00
Total Funds at book value, November 11, 1961		$1,047,268.29

JACOB H. VASTINE, 2ND, M.D.
Treasurer

Annual Report on the Library*

ADMINISTRATIVE

Vintage Year. The watering of the roots and the cultivation of the soil during previous years seems to have produced a vintage year of tangible harvest. The response to the S. Weir Mitchell Associates program evinces a considerable reservoir of good will toward the College. Substantial increases in the use of the library and income from a variety of sources suggest a growing awareness both of the benefits derived from its services and of the fiscal nourishment required for its healthy development.

S. Weir Mitchell Associates. The promises of generous yield hopefully presaged in last year's report have been happily realized in good measure. At the close of the fiscal year the number of S. Weir Mitchell Fellows had increased from twenty-two at the onset to fifty. The enthusiastic response to this means of perpetuating evidence of one's concern for the stability of the library has been widespread enough to guarantee continuing additions to this group of benefactors during the coming year. Particularly encouraging has been the breadth of interest demonstrated by the variety of journals chosen for endowment. Special group dinners and a dedicated committee have accelerated the success of the S. Weir Mitchell Associates.

Income Increment. Major gains were achieved in the following sources of library income: Contribution Plan, Medical Documentation Service, and Photoduplication. An increasing number of the library's institutional friends are demonstrating their desire to share the costs of the library to which they turn for medical literature. The number of non-profit institutions contributing to the support of the College library rose from six in 1958–59 to eleven in 1959–60 and to seventeen this year. Revenue from all library registrations, individual and institutional, non-profit and commercial increased from $11,622.75 in 1958–59 to $16,317.25 in 1959–60 and to $18,963.48 this year.

An account of the fiscal stature and productivity of the Medical Documentation Service is offered in the section of this report written by its Director.

The apparently orbiting course of photoduplication work has varied between an apogee of 7,481 and a perigee of 3,845 pages reproduced per month. The gross revenue from this department rose from $2,371.12 in 1958–59 to $5,295.49 in 1959–60 and $17,553.11 in the year just completed.

Library Use. It was expected that the phenomenal growth of photoduplication requests would be mirrored by a decrease in the number of volumes actually withdrawn from the library on the assumption that the duplications would frequently be accepted as substitutes for borrowing the original. The fallacy of this reasoning is demonstrated by the increase in the number of volumes borrowed by other institutions (interlibrary loan) from 13,359 to 14,780. The total number of volumes withdrawn by all classes of library users rose by twenty-five percent. It would seem as if growth begets growth.

Size of Staff. The component of the library which has showed the slowest rate of growth during the past decade has been the staff itself. During a period when photoduplications have increased twenty-two-fold, interlibrary loans have increased eight-fold, the number of serials currently received has almost doubled, and the number of volumes circulated from the library has almost trebled, the size of the library staff, exclusive of the Medical Documentation Service, is only one-half again as large. At the beginning of the year provision was made in the budget for one new staff position and after the close of the current year there was a firm prospect of two additional positions for the year to come.

* November 1, 1960–October 31, 1961.

Physical Plant and Equipment

A number of new workaday tools were purchased to increase the efficiency and pleasure of library operation. Funds from the Smith Kline & French Foundation grant were used for a separate desk for the Reading Room staff. New shelving was built adjacent to the circulation desk to hold volumes which are awaiting pick-up by messengers. In the Periodical Room the purchase of a new Kardex unit was required to supplement the existing units, to provide for the increased number of titles currently being received. A magazine display rack was also bought to provide exhibition space for copies of new titles not previously received by the library. A postage scale was acquired, to facilitate the mailing of photoduplications and interlibrary loan packages. A postage meter system was installed, to reduce petty cash turnover and to speed the mail. A new book truck was procured for the Xerox operator.

Lighting. The Library contingency fund, originally secured for the library by T. Grier Miller, M.D., was tapped, to bring new lighting fixtures into the Medical Documentation Service office, a study room, and the Librarian's office.

Euphoria. Lest the readers of this report conclude that the Library Administration is completely captivated by the pleasures of a vintage year, we hasten to reaffirm our realization that modern science libraries must run hard to remain in the same place. Comfort has been derived from the quotation by the President of the College in last year's report of S. Weir Mitchell's reminder that, "you see, therefore, how large, how varied, how expensive are the wants of a great library—yet you must in reason expect your library to make even larger demands for money. It is an expensive necessity."

Sealing Wax and Kings

Visitors. The library staff enjoyed participating in the hospitality extended to the Freshman medical students from Hahnemann Medical College, Temple University, and the Woman's Medical College upon the occasions of their traditional visits to acquaint themselves with the facilities of the College. New students in the University of Pennsylvania Graduate School of Medicine joined the groups who visited the library for the first time this year. Because of the large numbers involved, the students were lectured to and toured in three sections.

Another group which absorbed a somewhat stiffer dose of library policy and procedure was a class from the School of Library Science of Drexel Institute of Technology. Different interests were manifested by a group which visited the College under the auspices of the Council of the International Visitors and the American College of Physicians. These "tourists" were mostly foreign medical personnel with temporary duty assignments in this country. The administrative staff of the College also enjoyed the privilege of participation in a program at the College upon the occasion of the meeting of the Association of Clinical Sciences, which was held in Philadelphia this year.

The visitors from the farthest distances away were the three Medical Library Association Fellows who were studying in the United States this year with assistance from the Rockefeller Foundation. These touring medical librarians were from Norway, Ghana, and the Territory of Papua and New Guinea.

Volunteer help. In one of his letters to the Fellows of the College, the President suggested that some of their wives might be interested in offering some volunteer help to the library. Mrs. George Farrar responded to this suggestion and was most helpful in the program of mending books.

Library hours. At the beginning of the Fall season the library's traditional hours of opening (9:30 to 5:30) on Tuesday, Thursday, Friday and Saturday, were changed to 9:00 to 5:00. Previous Monday and Wednesday hours (9:30 a.m. to 9:30 p.m.) were altered to provide for opening from 9:00 a.m. to 9:30 p.m.

The new hours now coincide with the hours of opening of most of the other local libraries which telephone interlibrary loan requests in the morning. The extra half-hour permits the gathering of the material from the stacks in time for the messengers, who frequently arrive near midday. Announcements of the proposed change were publicized in the library's *Booklist* well in advance, in order to encourage comment from the Fellows and others. In general, the response was most favorable.

Wood Room. The Wood Room was redecorated under the expert supervision of Mrs. Thomas M. Durant. Included in this revitalizing procedure were the re-rushing of the chair seats, a new rug, and a fresh coat of paint.

Eberhard Foundation. The College library was able to continue its subscription to *Chemical Abstracts* thanks to a grant from the Eberhard Foundation which provided one half of the cost of this important reference tool. The unique refusal of the American Chemical Society to recognize the educational function of the College library results in an annual subscription cost of $950.00, in contrast to more moderate rates offered to teaching institutions.

Special donors. It is fitting to single out one particular group of library supporters from the list which appears at the end of this report. These individuals and institutions give the library books and journals which would otherwise be discarded. Frequently this material is received by these donors as an exchange for their publication. In many cases these are the only sources from which these titles are obtained by the library, and in other instances the material is arranged and stored in the library's duplicate collections, where it is made available to other libraries in the area. Special thanks are due to: the American College of Physicians, Samuel Bellet, M.D., Institute of the Pennsylvania Hospital, Jefferson Medical College, Richard A. Kern, M.D., Lea & Febiger, Lee Ramsdell & Co., Abram H. Persky, M.D., the Philadelphia College of Pharmacy and Science, W. B. Saunders Co., Smith Kline and French, Temple University School of Medicine, Wistar Institute, and the Woman's Medical College.

Personnel

Mrs. Elnora Smith resigned from the position of Reference-Circulation Librarian in June to accept a position in the Levittown, N. J. Junior-Senior High School, which is nearer her home. This vacancy was filled in September by the appointment of Miss Marcia Davidoff, who had previously been employed by the Schenectady County Library and the Sterling-Winthrop Research Institute. During the summer interregnum temporary help was provided by Miss Carolyn Stark and Miss Nora Reiner, students at Bryn Mawr College. Miss Stark also worked part-time as a book mender.

Mrs. Dolores McFadden resigned as Library Secretary in May for a career of domesticity. Her position was filled through the appointment of Miss Carole Lynn Smith.

Mrs. Marion I. Schmieder was appointed to the newly created position of Assistant Serials Librarian in September. She previously was the Librarian at the Graduate Hospital. Mr. Norton Manoff was temporarily employed as a Serials Assistant.

Miss April Nelson, a student at Gallaudet College, did two weeks of practice work at the College library as part of her course of studies.

Daniel Cavanaugh, Jr. and William Messner, Jr. resigned from the paging staff. These positions were filled by the appointments of Edward Romasko, Jr., and Francis Kelleher.

Professional Staff Activity. The Medical Library Association is being served by library staff members in the following positions: Miss Muriel Hodge completed her two-year term as Placement Officer. Mr. Morse is chairman of the Sub-Committee on Bibliography. Muriel Zeldis was chairman of the Nominating Committee of the Philadelphia Regional Group of the Medical Library Association.

The library was represented at the annual meeting of the Medical Library Association, which was held in Seattle, by Miss Muriel Hodge and Mr. Elliott H. Morse. Mr. Morse served as an Instructor-leader during the ad-

vance seminar which was held before the convention. He presented a paper entitled "On Demand Copying" to the convention and addressed the Medical Society Libraries Group on the subject, "The Medical Society Library's Service in an Urban Community." The two papers will be published in the *Bulletin of the Medical Library Association.*

Mr. Morse is serving on the Budget and Finance Committee for the Second International Congress on Medical Librarianship, which will be held in Washington, D. C. in 1963. He participated in a panel discussion of the applicability of machine methods to library information services at a meeting of the Special Libraries Council of Philadelphia and Vicinity. Other activities included the preparation of a tape for later broadcast, on the subject of librarianship as a career, for the Drexel Institute of Technology; and participation in a program of the Delaware Valley Chapter of the American Documentation Institute on copyright.

Mr. McDaniel's activities are noted in the historical section of this paper.

Benefactors. A list of donors of books and other library materials appears in the statistical section of this report.

The library is pleased to be able to report the following institutional subscriptions in support of the library.

NON-PROFIT INSTITUTIONS

Antioch College
Bryn Mawr Hospital Medical Staff
Children's Hospital of Philadelphia
Graduate School of Medicine of the University of Pennsylvania
* Hahnemann Medical College
Harrisburg Hospital
Institute for Cancer Research
Jefferson Medical College
Lankenau Hospital
Philadelphia General Hospital
* Seton Hall College of Medicine and Dentistry
Temple University School of Medicine
U. S. Naval Hospital Staff, Philadelphia
University of Pennsylvania School of Medicine
Walson Army Hospital Staff
Woman's Medical College of Philadelphia

* Received after the close of the fiscal year.

COMMERCIAL INSTITUTIONS

Air-Shields, Inc.
Atlas Chemical Corp.
Barnes, Dechert, Price, Myers & Rhoads
Beasley & Ornsteen
Bell Telephone Company
Bernstein & Bernstein
Borden Company-Chemical Division
Campbell Soup Company
Dentists' Supply Co.
Dilworth, Paxson, Kalish, Kohn & Dilks
E. I. du Pont de Nemours, Haskell Laboratory
E. I. du Pont de Nemours, Lavoisier Laboratory
E. I. du Pont de Nemours, Stine Laboratory
Jerome Edelman
Freedman, Landy & Lorry
General Electric Co., Missiles & Ordnance Systems Dept.
Gray & Rogers
Halbert & Kanter
Harvey & Thomas
Institute for Scientific Information
Kontes Glass Co.
La Wall & Harrisson
Lee Ramsdell & Co.
Lewis & Gilman, Inc.
MacAndrews & Forbes Company
McNeil Laboratories
Mead Johnson & Co.
Medical Literature, Inc.
Merck Sharp & Dohme
Morgan, Lewis & Bockius
Mulford Colloid Laboratories
National Drug Company
Norwich Pharmacal Co.
Ortho Pharmaceutical Corp.
Oxy-Catalyst Inc.
Pennsylvania Railroad Company
Chas. Pfizer & Co., Inc.
Prudential Insurance Co.
Quaker Chemical Products Corp.
Radio Corporation of America
Richter, Lord & Levy
Rittenhouse Book Store
A. H. Robins Co., Inc.
William H. Rorer
Rohm & Haas Company
Samson Laboratories
Smith Kline & French Laboratories
E. R. Squibb & Sons
Arthur H. Thomas and Company
Wallace Laboratories
Warner-Lambert Laboratories
Wyeth Laboratories

E.H.M.

Historical

Historical Cataloguing Project. Owing to personnel problems, the project's course during the year was fitful. Nevertheless, thanks to the cheerful pertinacity of the cataloguer, Mrs. Maria A. Shchuka, and her assistant, Miss Hildegard Gutzmann, some progress was made. Those acquainted with the time-consuming factors involved in historical cataloguing will not be inclined to under-rate, under the circumstances, their full cataloguing of 157 titles, with the attendant re-cataloguing of 15 closely linked ones, and correction of 457 cards. The total number of cards typed was 939. The Project will continue, as such, under unavoidably reduced steam, until the grant from the American Philosophical Society which made it possible is exhausted. Developments subsequent to the stated closing-date of this report happily give promise of aid and issue to the Project.

J. Monroe Thorington, M.D.—Benefactor. Dedicated followers of the fortunes of the library's historical section will readily recall that its reports have repeatedly expressed gratitude to Dr. Thorington for making possible the acquisition of important historical items. Towards the close of the library year this generous Fellow assured the indefinite maintenance of his support by donating the sum of $5,000 to the College, specifying that the income should be used for the development of the historical collections. A donation of this magnitude, as it happens, automatically leads to the inscription of the donor's name in the golden roll of 'Benefactors' that may be seen in the vestibule of the College building. Thus, through roll and bookplates, present and future users of the historical collections may be reminded of one continuously aiding their studies; those close to the administration of the library, of course, will need nothing in the nature of an *aide-mémoire.*

Acquisitions. A number of acquisitions of more than passing interest were noted in n.s., no. 47 (July, 1961), of the *Fugitive Leaves*; and in the January, February, April, September, and October, 1961 reports of the Library Administration. The palm for rarity must unquestionably be awarded to an apparently unrecorded Galenic *Que in hoc volumine continentur* edition printed in Pavia, 1510, by Jacobo de Burgofranco. It contains translations of, and commentaries on, Galen's treatise on medical practice—called, variously, *Microtechne, Tegni, Ars parva, Ars medica, etc.*—by Haly Eben Rodan (11th c.) and Jacob of Forlì (14th/15th cc.). The contents page is headed by a large woodcut showing the three medical giants of the Middle Ages—Galen, Avicenna, and Hippocrates—seated side-by-side, with open books in their laps, and Hippocrates holding up the traditional urinal. This edition would seem comparable in important respects, but not identical, with one printed in Pavia in 1501. Aiding in its purchase were the Section on Medical History, and two of its members, individually, Drs. Samuel X Radbill and Fred B. Rogers. To both of the latter the historical collections are further indebted for vigorous and generous support rendered in a number of ways.

Fugitive Leaves. There were seven issues within the year under review. N.S., nos. 42–43 supplied a list of 18th c. American medical students at the University of Leyden, supplementing the Edinburgh list offered in 1958/59; the former served incidentally to remind us that the first president of the College, John Redman, was a Leyden graduate (1748), that his diploma hangs in the Packard-Krumbhaar Medical Historical Alcove, and that the historical collections contain copies of his thesis. No. 44 presented translations of passages in the works of two noted medieval surgeons (Lanfranchi and Guy de Chauliac) setting forth their views on the proper qualifications for a surgeon. Nos. 45–46 made public a serendipitously discovered letter of considerable interest from John Morgan to William Hewson, which had the benefit of a commentary by Whitfield J. Bell, Jr. No. 47 was the 'Acquisitions' number referred to above. No. 48 started publication of the contents of the library's oldest extant catalogue, a manuscript one compiled in 1818.

Exhibits. Exhibits were arranged for meetings, at the College, of the Society of Clinical Surgery, the Association of Clinical Scientists, and, of course, the Section on Medical History. Other exhibits included one based on the library's first catalogue, mentioned above, and one commemorating the centenary of the first publication of Morgagni's *De sedibus et causis morborum.* Towards the close of the year, the Superintendent, Mr. George S. Allen's able installation of lighting fixtures in one of the cases added immeasurably to the pleasures of an exhibit of medicinal plants on postage stamps, arranged from his collection by Dr. Henry A. Arkless, a Fellow of the College—and to many pleasures obtainable from subsequent exhibits. After the close of the year, the second exhibit case, and later exhibits, were similarly, most helpfully, illuminated.

Curatorial wanderings. During the year, the curator completed a tour of duty on the Osler Medal Committee (latterly, as its chairman), American Association for the History of Medicine; and the Murray Gottlieb Prize Committee, Medical Library Association. In April, he read a brief paper on the history of the College at a dinner meeting, in the College, of the Association of Clinical Scientists. In May, at a special convocation of the University of Louisville, held in honor of Dr. Emmet Field Horine, whose *Daniel Drake* was then being issued by the University of Pennsylvania Press, he gave an address entitled "The Medical Liaison between Louisville and Philadelphia"; and, during his stay, also delivered the T. Cooke Smith Lecture of Louisville's Innominate Society.

W. B. McD., 2d

Medical Documentation Service

The year 1960–1961 has been one of completion and continuation rather than of dramatic growth. We completed abstracting projects for the Cancer Chemotherapy National Service Center of the National Institutes of Health, for Biological Abstracts, and completed editorial, indexing and allied services relating to a comprehensive bibliography of influenza for the American Institute of Biological Sciences. We continued to report references for monthly abstracting publications of the National Foundation (viral diseases, congenital malformations, and the etiology of arthritis and rheumatism). We continued to supply the textual matter for "An Annotated Bibliography of Influenza." We also continued to supply references, abstracts and annotations to individual practitioners and investigators as well as to pharmaceutical manufacturers.

Our staff has been remarkably constant and faithful. Robert E. Asnis, Ph.D., has been concerned with abstracting and translating and has maintained a high standard as well as an increased volume. Mrs. Jean Stevens continued efficiently as executive secretary and was assisted by Mrs. Margaret Holloway, Mrs. Jean Buechell, Mrs. Eileen Phillips and Mr. Julius J. Williams.

Our activities can be given in summary as follows (1959–60 figures in parentheses):

Average number of subjects scanned per month	28	(29)
Total references reported	8416	(9162)
Approximate number of clients (scanning)	16	(20)
Abstracts prepared	2400	(5642)
Bibliographies prepared	281	(193)
Translations	300	(140)

It will be seen that our scanning service has declined. This may possibly be due in some part to the publication of new abstracting journals. Our income from scanning, $11,000, was, however, almost identical to that received in 1959–60. The decrease in the total number of abstracts prepared is accounted for by the termination of the contract with Biological Abstracts and the completion of the cancer abstracting.

The gross income was approximately $38,000 of which (round figures) $9,800 came from abstracts, $4,200 from searches, $11,000 from scanning, and $7,000 from translations. We paid out about $24,000 in salaries to our regular and part-time employees and about $5,500 to sub-contractors. Our balance of income over outgo was thus more than $7,000.

Our accounting procedures consider the Service an integral part of the Library and no bookkeeping charges are made for administrative overhead, rent, telephone and certain supplies and postage.

We believe the need for services specifically designed to meet the requirements of individual clients will continue to justify the operation of the Medical Documentation Service.

W.L.B.

STATISTICAL SUMMARY

Inventory

	1961		1960	
Accessioned items[1]				
Incunabula[2]	420		420	
Manuscripts and typescripts	1,208		938	
General	207,172		202,942	
Accessioned pamphlets	4,699		4,628	
		213,499[3]		208,928[3]
Unaccessioned items[1]				
Reports	28,799		28,794	
Theses	60,411		60,158	
Pamphlets and reprints	231,499		231,472	
		320,709		320,424
Portraits[4]		104,639		103,828

Current Serials

	Subscription	*Gift*	*Exchange*	*Total*
U.S.A.	377	427	67	871
Western European Continent	644	81	125	850
Latin America and West Indies	35	83	75	193
United Kingdom and Eire	138	25	27	190
Canada	9	15	10	34
Eastern European Continent	96	48	33	177
Asia (including Japan)	21	75	57	153
Africa	2	9	14	25
Pacific (including Australasia)	3	10	5	18
United Nations	9	1		10
International	23	8		31
Grand Total: 1961	1,357	782	413	2,552
Grand Total: 1960	1,219	701	405	2,325

New Titles: A total of 205 serials was added in 1960/61.

Separate issues received, checked in on the cards, and shelved totaled 20,801. In addition, thousands of duplicate issues were received as usual. No attempt was made to count those held merely for exchange or other use.

Visitors in the Norris Room for the year totaled 3,569.

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[1] Accessioned items in this library comprise the total number of bound volumes and such unbound pamphlets as have been cataloged as separate bibliographical units regardless of their size.

There remain many thousands of unaccessioned pamphlets awaiting accessioning and cataloging. A true quantitative and qualitative picture of the library's holdings cannot be presented until this wealth of neglected material has been processed and duly registered in our 'accessioned' or 'volume,' count.

[2] The library owns 422 incunabula, but there are two cases of two bound together, reducing the number of accessioned items.

[3] Included in this figure are the following collections which are on permanent deposit in the library: Gross Library, 3,976 accessioned and 4 unaccessioned items; Parry Library of the Obstetrical Society of Philadelphia, 217; Mütter Museum, 200 (Mütter Museum books may not be removed from the College building).

[4] Including 124 oil, and 268 other, framed portraits in the care of the Committee on College Collections. The count of portraits represents the number of entries on the cards in the portrait catalog. The entries represent, in turn, both loose portraits and those in books, many of them, of course, being merely different reproductions of a single original.

Readers' Use of the Library

Library Hours. The library was open, during the academic year, from 9:30 to 9:30 on Mondays and Wednesdays, from 9:30 to 5:30 on the other weekdays. During June, July, August, and the first half of September, the library was open from 1 to 9:30 on Tuesdays; from 9 to 5 on the other weekdays, except Saturdays, when it was closed. In the second half of September, and in October, 1961, the hours were 9 to 9:30, Mondays and Wednesdays, 9 to 5, other weekdays. The following legal holidays were observed: Thanksgiving, Christmas and New Year's, Memorial, Independence, and Labor Days.

Visitors to Reading Room:

	Totals
1961:	11,603
1960:	9,694

Circulation:

	Totals	*Intra-mural*[5]	*Extra-mural*[6]	*Books*	*Journals*
1961:	67,168	45,406	21,762	10,440	56,728
1960:	63,181	45,792	17,389	12,010	51,171

Interlibrary Loans: The library sent 16,035 (1960: 13,359) volumes on interlibrary loan to 250[7] (1960: 91) libraries in 32 (1960: 35) states, including Washington, D. C., and Canada, and has borrowed 3 (1960: 15) volumes from 2 (1960: 4) libraries.

Photoduplications: 67,547 pages were photoduplicated on request (1960: 19,357).

Accessioned Acquisitions:

1961: 4,571 volumes (2,538 by purchase; 1,585 by gift; 448 by exchange).
(Books: 1,518; Periodicals: 2,982; Pamphlets: 71).
1960: 4,070 volumes (1,957 by purchase; 1,697 by gift; 416 by exchange).
(Books: 1,264; Periodicals: 2,686; Pamphlets: 120).

Non-accessioned Acquisitions:[8]

1961: 5 Reports (1960: 1)
253 Theses (1960: 395)
21 Miscellaneous items (1960: 62)

Donations

The donors for the past year number 156 (1960: 117). The library is indebted for large gifts of books, pamphlets and unbound periodicals to the following donors: Children's Hospital of Philadelphia; F. A. Davis Co.; Jeanes Hospital; Dr. R. A. Kern; Lea & Febiger; J. B. Lippincott Co.; National Foundation for Infantile Paralysis; Pennsylvania Tuberculosis & Health Association; W. B. Saunders Co.; Smith Kline & French Laboratories; Wallace Laboratories.

Various publishing houses, among the large group of corporate donors, have presented volumes as follows: F. A. Davis Co., 11; Lea & Febiger, 4; J. B. Lippincott Co., 43; W. B. Saunders Co., 77.

Other individual donors were as follows: Drs. F. K. Alexander, C. H. Alstein, J. Appleyard, H. A. Arkless, J. H. Arnett, H. S. Arthur, O. V. Batson, E. L. Bauer, W. J. Bell, Jr., S. Bellet; Mrs. H. A. Berkowitz; Drs. K. R. Boucot, W. N. Bradley; Dr. & Mrs. T. Butterworth; Drs. B. Chance, K. S. Chouké, A. P. Cifarelli, G. Claton; Miss E. Coates; Mrs. M. Solis-Cohen; Drs. P. C. Colonna, E. F. Corson, A. M. Dannenberg, Jr., T. L. Dehne, G. G. Duncan, I. I. Edgar, O. S. English, J. T. Freeman; Miss E. Fryer (bequest); Dr. J. F. Fulton; Mrs. E. S. Gault; Drs. H. A. Gilda, T. N. Haviland, M. Helpern, C. Hovey, G. W. Huggler, E. T. Johnson, J. V. Klauder, J. A. Kolmer, D. W. Kramer, E. B. Krumbhaar; Mrs. E. O. E. Lan; Mr. W. R. Le Fanu; Drs. W. Levy, E. R. Long, C. G. Looski, S. M. McCann; Mr. W. B. McDaniel, 2d; Mrs. M. Macdonough; Drs. R. H. Meade, G. Miller,

[5] The number of volumes "consulted in the library" includes only those supplied on demand. Readers have access to the bound volumes of periodicals and reference works kept on the shelves in the Reading Room; the Fellows, and occasionally others, by special permission, have access to the book-stacks. There are, therefore, many volumes consulted of which no accurate record can be kept.

[6] This figure includes 5,574 unbound current issues circulated from the Periodicals Room.

[7] This figure includes 36 commercial institutions which are registered borrowers.

[8] As usual, not all the pamphlets, theses, and numbers of various journals listed as received have been checked for keeping or discard at the close of the library year.

T. G. Miller, M. R. Milligan, W. L. Mills, M. Naide, S. W. Newmayer, E. H. Nickman, G. W. Norris, N. Padis; Prof. A. Pazzini; Drs. E. P. Pendergrass, O. H. Perry Pepper, A. H. Persky, H. Pettit, G. P. Pilling, S. X. Radbill, J. E. Rhoads, F. B. Rogers, S. Rubin, H. G. Scheie, T. G. Schnabel; Mrs. H. P. Schneider; Section on Medical History; Drs. F. C. Sharpless, L. E. Snodgrass, P. Spaeth; Mrs. A. C. B. Steel; Dr. P. E. Steiner; Mrs. W. D. Stroud; Drs. J. M. Thorington, S. N. Turiel, A. S. Unver, M. E. Vogt, M. H. Wendkos, G. L. Wilbar, Jr., J. R. Willson; Mrs. G. B. Wood; Drs. H. B. Wood, D. D. Zimring.

The *Transactions & Studies* was sent, either in exchange or as gift, to 505 organizations.

Theses and dissertations to the number of 250 have been received on exchange from the following European schools of medicine: Universities of Basel, Bern, Lausanne, Leiden, Liége, Louvain, Lund, Uppsala.

THE STAFF[9]

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[9] Library staff list as of February 1, 1962.

Annual Report of the Committee on the Mütter Museum and College Collections

THE Mütter Museum of the College of Physicians is open daily, with the exception of Saturdays and Sundays, from 9 a.m. to 1 p.m., and from 2 p.m. to 4 p.m.; and on the nights of the stated monthly meetings of the College it is open until 7:30 p.m., with the Curator in attendance.

During the past year there were 2052 visitors to the Museum, many of them from foreign countries. Local public schools were represented by classes from Clifton Heights High School and Gillespie High School. Student nurses from the Montgomery Hospital in Norristown made their yearly visit and the first year classes from Hahnemann Medical College, Woman's Medical College, Temple University School of Medicine, and St. Leonard's Academy also attended. A group from the West Chester State College and the biology students from Drexel Institute paid initial visits and were much impressed with the extent of the material on display. While the Franklin School of Science and Arts did not send large groups this year, there were not many days when from five to ten students from this school did not come to inspect the exhibits that had been called to their attention by instructors or classmates.

Those in charge of the Museum feel that they have been of service this year to many persons not connected with the College. Upon request several items that were in College Collections, and so did not come under the restrictions of the Mütter Museum Deed of Gift, were loaned to Dr. Kissen for a television program designed to alleviate the fears that many children have when taken to a physician, especially when it is for the purpose of receiving "shots." These instruments were all returned promptly and in good order, and, were it not for the clause in the will of Dr. Mütter that nothing once taken into the museum collection may ever again be removed from the building, many other items could serve a similar good purpose.

All of the instruments received from the estate of the late Dr. William Hewson could not be accepted because of duplication. These were offered to Dr. John B. Blake, Curator of the Division of Medical Sciences at the Smithsonian Institution, who gladly accepted them for his department.

The Armed Forces Institute of Pathology in Washington, D. C., accepted a number of wax models of skin diseases presented to the College by Jefferson Medical College, all of which we could not use.

The Muñiz Collection of ancient Peruvian skulls was made available to Dr. Stephen Podolsky, an intern at the Henry Ford Hospital in Detroit, Michigan. He spent two days in the museum with a photographer taking pictures of the skulls and collecting all available material on them for a paper he was writing.

Dr. Samuel X Radbill made his yearly visit with a group of graduate medical students in pediatrics from the University of Pennsylvania. Here they were shown early clinical thermometers, hypodermic syringes, stethoscopes, microscopes, and infant feeding spoons, dishes and bottles. Dr. Radbill brought many examples of infant feeding vessels from his own collection to exhibit with the few that are in the Museum, and like all good collectors, we find that each year he has augmented his collection with new items. These classes, each year consisting of doctors from different foreign countries, is one of the most interesting as well as one of the most interested to come to the museum, for they are intrigued by many of the instruments not found in their own countries.

This year, although displayed in the Museum, all accessions were catalogued in the

College Collections where they may be loaned upon request.

The 73rd Thomas Dent Mütter Lecture was delivered December 7, 1960 by Dr. Robert Blizzard, substituting for Dr. Lawson Wilkins who was ill. The title of the address was, "Abnormalities of Sex Differentiation; Classification, Diagnosis and Treatment". The 74th Thomas Dent Mütter Lecture was given by Colonel Joe H. Blumberg, M. C., U. S. A., on December 6, 1961, his lecture being, "Laboratory Medicine in Russia."

Mrs. Ella N. Wade was reappointed Curator for the year 1961–62.

College Collections

During the year the Committee on College Collections supplied the Medical History Museum in Melbourne, Australia, with copies of the Supplement of the Medical Medal Catalogue, and was able to furnish Dr. Paul Kreider of Springfield, Illinois, with a print of the photograph of Jules R. Péan.

Since only three portraits, namely those of Benjamin Rush, Isaac Hays and George W. Norris, needed restoring by Mr. Frank Ireland, some of the money appropriated for portrait repair was used to purchase new name plates for the portraits of William Thomson, Isaac Hays and John A. Monges.

Among the accessions to College Collections this year is a dainty statuette of Imhotep, an authentic reproduction of the original in the Museum of Fine Arts in Boston, Massachusetts, presented by *Dr. Fred B. Rogers. Dr. Rogers* also presented a heavy bronze apothecary mortar and pestle. This mortar is dated 1601 and inscribed, "Love God above All", in Middle German.

Two small 18th century pharmacy jars from the village of Meillonas, near Bourgen-Bresse, France, were donated by *Dr. J. Monroe Thorington*, and *Dr. Samuel X Radbill* kindly parted with two of his infants' feeding bottles used in the 18th century, and a crude iron medicine spoon of about the same period.

From the estate of the late *Dr. William Hewson* we received an unusual microscope, Esmarch's chloroform mask, Luer's chain ecraseur, and Dr. Oliver's portable mercurial compressed air manometer.

Miss Margaret Beattie of California presented an interesting collection of Chinese surgical instruments that were purchased by Dr. R. A. Bolt in Korea in 1912.

A rectal dilator was sent to the College for the collection by *Dr. Irvin M. Gerson.*

Mr. Thomas G. Hull of Yarmouth Port, Massachusetts, sent us a large box of badges. Some were American Medical Association items, and others were various national and state badges. The A.M.A. items were the only ones with the illustrated metal pendant, so these were all that were accepted since the celluloid cards on the others were of little interest. This donation made it possible for us to add many that were missing in the A.M.A. collection of the College, and to also offer quite a number of duplicates to the Smithsonian Institution, which they gladly accepted, noting "they represent a phase of Medical History in this country."

Many of the instruments that were not accepted during the year because of duplication were made available to medical students.

Mrs. Ella N. Wade was reappointed clerk-technician for the year 1961–62.

A. Reynolds Crane, M.D., Chairman

Transactions of the Sections

SECTION ON GENERAL MEDICINE

23 October 1961

Histopathological Classification of Periarteritis Nodosa: A Review of 56 Cases. Roland W. Moskowitz, M.D.* (Discusser: Fred Urbach, M.D.*) (*Abstract 1*, below)

The Pathogenesis of Chloramphenicol-Induced Aplastic Anemia. Allan J. Erslev, M.D.,* and Ioulios A. Iossifides, M.D.* (Discusser: Arthur E. McElfresh, M.D.*) (*Abstract 2*, below)

Periodic Disease. Hobart A. Reimann, M.D.* (Discusser: Francis C. Wood, M.D.) (*Abstract 3*, below)

Histidinemia. Victor H. Auerbach, Ph.D.,* Angelo M. DiGeorge, M.D.,* Robert C. Baldridge, Ph.D.,* Charles D. Tourtellotte, M.D.,* and M. Prince Brigham, M.D.* (Discusser: Henry W. Baird III, M.D.*) (*Abstract 4*, below)

27 November 1961

The Intravenous Tolbutamide Test as a Diagnostic Aid in Carcinoma of the Pancreas. Donald Berkowitz, M.D., Leon Greenberg, M.D.,* and Sol Glassman, M.D. (Discusser: Ralph M. Myerson, M.D.) (*Abstract 5*, below)

Evaluation of the Antiarrhythmic Properties of Antazoline. Leonard S. Dreifus, M.D.,* Thomas S. McGarry, M.D.,* Yoshio Watanabe, M.D.,* S. Ronald Kline, M.D.,* Morton Waldman, M.D.,* and William L. Likoff, M.D. (Discusser: John Urbach, M.D.*) (*Abstract 6*, below)

Chlorothiazide Effects on Serum Lipids in Diabetic Patients. Sigmund R. Greenberg, M.D.,* Roy G. Klotz, Jr., M.D.,* and Paul M. Roediger, M.D.* (Discusser: C. Robert Tittle, Jr., M.D.*) (*Abstract 7*, below)

The Syndrome of Ruptured Chordae Tendinae. Joseph F. Uricchio, M.D., and Henry T. Nichols, M.D.* (Discusser: Dryden P. Morse, M.D.*) (*Abstract 8*, below)

22 January 1962

The Occurrence of Serious Hemorrhagic Complications of Anticoagulant Therapy. Bernard H. Pastor, M.D.,* Myron E. Resnick, M.D.,* and Theodore Rodman, M.D.* (Discusser: William L. Likoff, M.D.) (*Abstract 9*, below)

Hypocalcemia and Hypophosphatemia Accompanying Osteoblastic Osseous Metastases: Studies of Calcium and Phosphate Metabolism and Parathyroid Function. George D. Ludwig, M.D.* (Discusser: Howard M. Rawnsley, M.D.*) (*Abstract 10*, below)

The Use of Thyrotropin in the Assessment of Thyroid Function. Bertram J. Channick, M.D.* (Discusser: John H. Nodine, M.D.*) (*Abstract 11*, below)

The Clinical Significance of Simultaneous Pleural and Venous Glucose Determination, James E. Clark, M.D.* (Discusser: Harold L. Israel, M.D.) (*Abstract 12*, below)

SECTION ON MEDICAL HISTORY

18 April 1961

A Student's Note Book from William Osler's Clinics in Philadelphia. Samuel X Radbill, M.D. (*Transactions & Studies*, October 1961)

Thomas G. Morton and Blood Transfusion: 1869–1878. William D. Sharpe, M.D.* (*Transactions & Studies*, January 1962)

John R. Young: Medical Student Research in 1803. Frank P. Brooks, M.D.

21 November 1961

The Early History of the Cerebral Ventricles. Edwin Clarke, M.D., M.R.C.P.*

* By invitation.

The Influenza Pandemic of 1918. Francis C. Grant, M.D.

Acupuncture and Other Forms of Counterirritation. Frank A. Elliott, M.D., F.R.C.P.*

16 January 1962

On a Road in Normandy . . . 17 July 1944. Richard A. Davis, M.D.* (*Surgery, Gynecology & Obstetrics 113:* 242–254, August 1961.)

University of Pennsylvania School of Medicine in the Civil War. Alan C. Davis* (*Medical Affairs, University of Pennsylvania 2:* 1–95, Spring 1961.)

'Typhus' of Surgical Wounds in the War Between the States. H. Taylor Caswell, M.D.

SECTION ON OPHTHALMOLOGY[1]

16 March 1961

The Ocular Penetration of Declomycin. Dana Newton, M.D.,* Francis P. Furgiuele, M.D.,* and David Seaman, M.D.*

Complications of Photo Coagulation. Edward J. Cannon, M.D.*

Malignant Exophthalmos: Report of a Case. Francis J. Gilroy, M.D.*

20 April 1961

The Physiological Significance of Gerontoxon, Especially in Younger Individuals. John K. Finley, M.D., and Donald Berkowitz, M.D.

Evisceration Following Corneal Injury Induced by a Contact Lens. Edward H. Hanhausen, M.D.*

Neuro-Ophthalmological Implications of the Gerstmann Syndrome: Report of a Case. Robert J. Kirshner, M.D.*

19 October 1961

Problem of Retinal Detachment in the Presence of Glaucoma: Presentation of Two Cases. Lov K. Sarin, M.D.,* and James Chessen, M.D.*

Spontaneous Cure in Acute Narrow Angle Glaucoma: Report of Two Cases. William C. Frayer, M.D., and Harold G. Scheie, M.D.

Observations on Patients with Diseases Involving the Macula. Ruth E. Fabritius, M.D.*

16 November 1961

Cell Proliferation in Ocular Tissues. Ludwig von Sallman, M.D.,* National Institutes of Health, Bethesda, Md. (Twenty-fourth Annual de Schweinitz Lecture.)

21 December 1961

Immune Response of the Cornea to Herpes Simplex Virus. Theodore W. Sery, M.D.,* and Morton W. Richman, M.D.*

Hereditary Bilateral Essential Iris Atrophy. Michael I. Wolkowicz, M.D.*

Tension and Tonography in Children. Lov K. Sarin, M.D.,* Line Chevrett, M.D.,* and Irving H. Leopold, M.D.

18 January 1962

Cataract Extraction after Filtering Operations for Glaucoma. Harold G. Scheie, M.D., and J. Fraser Muirhead, M.D.*

Ophthalmoscopic Findings in Internal Carotid Artery Occlusion. Thomas R. Hedges, Jr., M.D.

Papilledema in a Two Year Old Child: Case Report with Pathologic Specimen. Richard M. Lubowitz, M.D.*

15 February 1962

Management of Retinal Detachment: Its Evolution through the Past Ten Years. Charles L. Schepens, M.D.,* Boston, Mass.

SECTION ON OTOLARYNGOLOGY[2]

15 March 1961

In Memoriam: Chevalier L. Jackson, M.D., Arthur J. Cracovaner, M.D.

[1] Abstracts of the presentation at this Section customarily appear in the *American Journal of Ophthalmology* and *A.M.A. Archives of Ophthalmology.*

[2] Abstracts of the presentations at this Section customarily appear in the *A.M.A. Archives of Otolaryngology.*

Histopathological Significance of Nasopharyngeal Tumors. Samuel M. Bloom, M.D.,* Mt. Sinai Hospital, New York City.

The Continuous Arterial Administration of Cancerocidal Drugs in Head and Neck Cancer. Robert D. Sullivan, M.D. (Discusser: Robert Glenn Ravdin, M.D.) (Joint Meeting in New York City of the Sections on Otolaryngology, College of Physicians of Philadelphia, and The New York Academy of Medicine.)

15 November 1961

Observations on Stapes Surgery for Otosclerosis: Clinical and Pathological. John R. Lindsay, M.D.,* University of Chicago (Joint Meeting of the Section on Otolaryngology, College of Physicians of Philadelphia, and the Philadelphia Laryngological Society.)

17 January 1962

Ruptured Aneurysm of the Left Internal Carotid Artery. Herbert P. Harkins, M.D. (Discussers: Robert K. Jones, M.D.,* and Louis E. Silcox, M.D.)

The Békésy Test in Otological Diagnosis. Richard A. Winchester, Ph.D.,* and Patricia J. Mellville, M.A.*

Chronic Middle Ear Disease and Its Management, and, The Surgical Transition in the Treatment of Otosclerosis. Philip E. Meltzer, M.D.,* Harvard University (First George M. Coates Memorial Lecture of The Philadelphia Laryngological Society.)

SECTION ON PUBLIC HEALTH, PREVENTIVE AND INDUSTRIAL MEDICINE

16 May 1961

Symposium on the Management of Chronic Mental Illness. William P. Camp, M.D.,* A. Victor Hansen, M.D.,* and Henry R. Rollin, M.D., D.P.M.* (*Transactions & Studies*, January 1962)

9 January 1962

Symposium on Periodic Multiphasic Screening Procedures. Katharine R. Boucot, M.D., M.P.H., Thomas W. Clark, M.D., Nicholas Padis, M.D., and Leonard W. Parkhurst, M.D.

Presentation of William Harvey Perkins Prize III (Medical Student Essay Contest Award) to Eugene L. Klenk, A.B.

ABSTRACTS

Abstract 1

Histopathologic Classification of Periarteritis Nodosa: A Review of 56 Cases. Roland W. Moskowitz, M.D., Department of Medicine, Temple University School of Medicine.

Fifty-six cases of necrotizing systemic arteritis were studied histologically. They were classified in three groups: Group 1 included 34 cases of necrotizing arteritis without associated pulmonary arteritis, necrotizing alveolitis, or numerous extravascular lesions; group 2 included 16 cases of pulmonary arteritis and either necrotizing alveolitis or numerous extravascular lesions or both; group 3 included six cases of so-called secondary periarteritis nodosa.

The numerous extravascular lesions in group 2 were similar to lesions associated with allergic disease processes, and contrasted greatly with the infrequency of extravascular lesions in group 1. Clinically, group 1 had a significantly higher frequency of hypertension and uremia than the other groups, while group 2 had a higher frequency of prior respiratory illness or allergic drug reaction as well as nasal granulomas, sinusitis, middle-ear infection, eosinophilia, and splenic vasculitis.

In group 2, lesions were classified as hypersensitivity angiitis and included Wegener's granulomatosis and allergic granulomatous angiitis as well as lesions similar to those described as allergic angiitis in the literature. Group 1 was felt to represent idiopathic periarteritis nodosa. Hypertension was considered as a probable contributing factor in the development of idiopathic periarteritis nodosa while prior respiratory illness or drug allergies were considered etiologic factors in hypersensitivity angiitis. The abnormal auto-im-

mune reaction of both groups may be similar; however, the sensitizing agent to which the patient responds abnormally appears to be different in selected cases.

Secondary periarteritis nodosa was considered to be a separate entity. The healing effect of steroids on periarteritis was confirmed in a study of 10 cases. It is felt that adrenal steroids act in a precipitating manner rather than as a specific cause of diffuse angiitis in patients with rheumatoid arthritis and systemic lupus erythematosus.

Abstract 2

THE PATHOGENESIS OF CHLORAMPHENICOL-INDUCED APLASTIC ANEMIA. Allan J. Erslev, M.D., Associate Professor of Internal Medicine, and Associate Director, Cardeza Foundation, and Ioulios A. Iossifides, M.D., Instructor in Pathology, and Associate Member, Cardeza Foundation, Jefferson Medical College.

Chloramphenicol is considered one of our most valuable bacteriostatic agents and is known for its relatively few toxic side effects. However, one of these rare side effects is the induction of a severe and frequently fatal bone marrow suppression.

Recent studies have suggested that a mild and reversible erythroid suppression may occur quite frequently during the administration of chloramphenicol and that the bone marrow utilization of iron is impaired regularly (1, 2). These studies indicate that the first signs of bone marrow toxicity is a change in the metabolic handling of iron.

In order to clarify the relationship between chloramphenicol and iron metabolism, *in vitro* studies were carried out on suspensions of human bone marrow or reticulocytes. Radioactive iron was used to measure the rate of cellular uptake of iron and cellular utilization of iron for hemoglobin synthesis.

It was found that the iron uptake by immature erythroid cells was suppressed by chloramphenicol and that intracellular utilization of iron was impaired. In view of the findings that chloramphenicol impairs iron uptake and iron utilization *in vitro* it seems probable that the early ferrokinetic changes observed *in vivo* after the administration of chloramphenicol are caused by a direct action of the drug on the erythroid tissue. The concentrations met *in vivo* are admittedly much lower than the concentrations utilized in these *in vitro* studies. Nevertheless, there is a straight line relationship between concentration and inhibitory action and it is possible that the low inhibitory activity at therapeutic levels if maintained long enough may lead to the changes observed *in vivo*.

The relationship between these regular disturbances in iron metabolism and the rare development of aplastic anemia is much more difficult to evaluate. It was found that a mere inhibition of iron uptake or intracellular iron utilization will not automatically lead to erythroid suppression or aplastic anemia. Lead, erythromycin, and tetracycline will all produce changes in iron metabolism *in vitro*, but are not known to cause erythroid suppression *in vivo*. However, within the class of the chloramphenicol-analogues there appears to be a good correlation between *in vivo* and *in vitro* toxicity.

If these changes in iron uptake and iron utilization are of pathogenetic importance it would be anticipated that patients receiving excessive doses of chloramphenicol would develop aplastic anemia. Excessive doses have indeed been shown to induce aplastic anemia (3), but the majority of patients who get into trouble have only received chloramphenicol in moderate well-accepted dosages.

An inborn or acquired error in the metabolic handling and excretion of chloramphenicol could explain the sporadic occurrence of bone marrow suppression. *In vitro* examination of known breakdown products revealed that they were all inert with the exception of one. However, this potentially toxic breakdown product is only found in trace amounts. It is, of course, possible that a faulty intermediary metabolism could result in the accumulation of large amounts of this product in the blood, a possibility which deserves further study.

An allergic pathogenetic mechanism has

been suggested, but humoral antibodies have never been demonstrated. This is actually not very surprising since tissue antibodies rather than humoral antibodies have to be incriminated in an allergic reaction against stationary bone marrow cells.

The most probable pathogenetic mechanism is an idiosyncracy at the cellular level. Only studies of patients who have recovered from chloramphenicol-induced aplastic anemia can elucidate this possibility. The *in vitro* technique described here should be employed since there is a justifiable reluctance to administer chloramphenicol to these patients. Such studies of the bone marrow *in vitro* may lead to information important for our understanding of the pathogenesis of chloramphenicol-induced aplastic anemia.

REFERENCES

1. Rubin, D. *et al.*: Changes in iron metabolism in early chloramphenicol toxicity. J. Clinical Investigation **37:** 1286, 1958.
2. Saidi, P. *et al.*: Effect of chloramphenicol on arythropoiesis. J. Lab. & Clin. Med. **57:** 247, 1961.
3. Kraboff, J. H. *et al.*: Effects of large doses of chloramphenicol on human subjects. New England J. Med. **253:** 7, 1955.

Abstract 3

Periodic Disease. Hobart A. Reimann, M.D., Department of Medicine, Hahnemann Medical College and Hospital.

Periodic disease, as presented before this Section in February, 1947, includes a group of disparate entities classified as periodic fever; periodic peritonitis; periodic (Quincke's, angioneurotic) edema; periodic synovitis (intermittent hydrarthrosis); periodic (Schönlein-Henoch, anaphylactoid) purpura; periodic myelodysplasia (neutropenia); periodic familial paralysis; and others. They are hereditary, begin at any time of life, recur episodically in precisely timed or irregular cycles, last for decades, do not interfere with the general health, resist treatment and are of unknown origin. More than 1000 cases are on record. Uncertainty exists if they are unrelated entities, or more likely, are unified by a universal, inherent, obscure rhythm. The rhythm. presumably is inapparent in most humans, but in some it may be exaggerated to provoke the respective periodic diseases. The clinical form the disease takes depends upon the specific sensitivity of the tissues affected, probably as a hereditary trait. Numerous features in common, including cerebral dysrhythmia, support the concept and point to the brain as the site of origin. Richter proposed that innate central and peripheral "biologic clocks" incite and regulate episodes. What excites the episodes and regulates periodicity is unknown.

Periodic peritonitis, because of its frequency, is the entity of current interest. It is known by eight names, one of which—familial Mediterranean fever—gives a wrong impression that it is geographically delimited, that it occurs only in Armenians, Jews and Arabs, and that it always is familial. Furthermore, abdominalgia, not fever, is the chief symptom. According to recent studies, it is a systemic disease with serositis, synovitis, vasculitis, hemic changes, cerebral dysrhythmia and hepatitis. Hyperglobulinemia occasionally leads to amyloidosis and death from renal failure.

For unknown reasons, a low-fat diet suppresses episodes in some victims. Among 14 patients so treated, episodes were stopped in 5, ameliorated in 4, and 5 were not benefitted. Paraminosalicylic acid, adrenal steroid hormones, colchicine and other drugs occasionally influenced episodes temporarily. If genetic factors are responsible for periodic disorders, there seems at present to be little hope for prevention or cure unless eugenic principles are applied.

Abstract 4

Histidinemia. Victor H. Auerbach, Ph.D., Angelo M. DiGeorge, M.D., Robert C. Baldridge, Ph.D., Charles D. Tourtellotte, M.D., and M. Prince Brigham, M.D. Departments of Medicine, Pediatrics and Physiological Chemistry, Temple University School of Medicine, and St. Christopher's Hospital for Children, Philadelphia, Pa.

Histidinemia is an enzymatic defect in histi-

dine metabolism resulting in the urinary excretion of histidine and a number of histidine metabolites, one of which, imidazolepyruvic acid, gives a positive ferric chloride test. This report describes studies performed on a child with an apparent deficiency of the enzyme histidase.

R. M. was a 4¼ year white female. She had been admitted to another hospital where, during evaluation of a febrile seizure, a urine specimen was tested with ferric chloride and gave a positive reaction. A provisional diagnosis of phenylketonuria was made until the plasma phenylalanine was found to be normal (2 mg.%). The child had developed normally except for small stature (size of average 2 year old) and slightly delayed speech. The results of clinical laboratory examinations were within normal limits except for urine specimens which gave negative to strongly positive reactions with ferric chloride solution.

Histidine in large amounts was detected in the urine by two-dimensional paper chromatography. Imidazole-pyruvic acid in the urine was identified and measured by formation of the enol-borate complex as described by Lin *et al.* Imidazolelactic acid and imidazoleacetic acid were located on two-dimensional chromatograms with diazotized sulfanilic acid reagent.

Plasma histidine levels were estimated by column chromatography and by a modification of the method of LaDue and Michaels. Formiminoglutamic acid (FIGLU) was determined by the enzymatic method of Tabor and Wyngarden. Urocanic acid and imidazolepropionic acid were identified by paper chromatography; the amount of urocanic acid was estimated spectrophotometrically by the absorbance at 277 mμ.

The patient excreted histidine, imidazolepyruvic acid, imidazolelactic acid and imidazoleacetic acid; since she did not excrete urocanic acid, imidazolepropionic acid or FIGLU, a block in the conversion of histidine to urocanic acid was apparent. Accordingly, experiments were performed in which histidine and urocanic acid were administered on separate occasions; the urinary metabolites were identified and measured.

The fasting plasma level of histidine was approximately ten times normal. After oral histidine loading (5 gm.), this level was further increased and remained elevated for four hours. Urinary excretion of imidazolepyruvic acid was markedly elevated after administration of histidine. The amounts of imidazolelactic acid and imidazoleacetic acid were also increased. Even under these conditions of loading with histidine, no urocanic acid, imidazolepropionic acid or FIGLU could be demonstrated in the urine.

Following intravenous injection of urocanic acid (920 mg.), urocanic acid and FIGLU were readily detected in the urine during the first five hour period. Neither metabolite was detected after 24 hours. In addition, imidazolepropionic acid and an unidentified metabolite were detected in smaller amounts.

Ghadimi *et al.* have recently described two siblings whose urine reacted with ferric chloride and who had elevated blood and urine histidine levels. One of these children showed mild retardation of speech development.

The evidence obtained is consistent with the supposition that the hepatic enzyme histidase, which converts histidine to urocanic acid, is lacking. It is probable that this is an inborn error of metabolism; however, the family data is insufficient to ascertain genetic mediation.

REFERENCE

1. Ghadimi, H., Partington, M. W., and Hunter, A.: A Familial Disturbance of Histidine Metabolism, New England J. Med. **265**: 221, 1961.

Abstract 5

The Intravenous Tolbutamide Test as a Diagnostic Aid in Carcinoma of the Pancreas. Donald Berkowitz, M.D., Leonard Greenberg, M.D., and Sol Glassman, M.D., Hahnemann Medical College and the Albert Einstein Medical Center.

In spite of many recent technics to help facilitate the diagnosis of malignancy, the early detection of pancreatic carcinoma continues to be a virtual impossibility. In the

search for another approach to the earlier diagnosis of this condition we have been interested in the evaluation of a new method to study carbohydrate metabolism in such patients since there is evidence at hand to indicate that impaired glucose tolerance is a common finding in this disease. The present study records our experiences with the use of intravenous tolbutamide to detect the presence of diabetes in a group of patients with proved malignancy of the pancreas.

Twenty five patients with suspected carcinoma of the pancreas who subsequently came to surgery were studied by means of intravenous tolbutamide. In addition, a three hour oral glucose tolerance test was done in each case. A control group of 25 apparently normal subjects was also tested with the intravenous technic.

Each patient in the control group showed a normal tolbutamide response. In 18 of the 25 patients with suspected pancreatic carcinoma this diagnosis was confirmed at operation. Tolbutamide responses were diabetic in 13 of these (72%). The glucose tolerance was abnormal in only 11 (61%). In 5 of the subjects with proved malignancy, both the tolbutamide and glucose tolerance tests were normal. Seven patients had no evidence of pancreatic disease at surgery. The tolbutamide and glucose tolerance tests were normal in each case.

The data thus suggest that the intravenous tolbutamide test may be helpful in the early detection of carcinoma of the pancreas by demonstrating the presence of diabetes and it appears to be more sensitive in this respect than the conventional oral glucose tolerance procedure.

Abstract 6

Evaluation of the Anti-Arrhythmic Properties of Antazoline. Leonard S. Dreifus, M.D., Thomas S. McGarry, M.D., Yoshio Watanabe, M.D., S. Ronald Kline, M.D., Morton Waldman, M.D., and William L. Likoff, M.D., Department of Medicine, Hahnemann Medical College and Hospital.

Antazoline, an anti-histaminic drug, was shown to have anti-arrhythmic properties in the dog. In this study antazoline was used in an attempt to abolish arrhythmias in 72 patients, including 15 with frequent atrial premature contractions, 48 with frequent ventricular premature contractions, 2 with atrial tachycardia with block, 2 with atrial flutter and 5 with atrial fibrillation.

The patients were examined daily, and the number of premature contractions heard over three minutes was recorded. Daily electrocardiograms were taken. The drug was administered orally in doses of 100 or 200 mg. three times a day.

Frequent premature contractions were reduced by at least 70% in 59 of the 63 patients studied. No effect was noted in patients with atrial tachycardia with block, atrial flutter or atrial fibrillation. After discontinuation of the drug, premature contractions recurred. This could be repeated with administration and withdrawal of the drug on several occasions.

Side effects were minimal and occurred in 5 patients; consisting of light-headedness in 3, nausea in 1, and drowsiness in 1. First degree A-V heart block was produced in 3 instances. There was no significant change in the QRS duration or the ST-T configuration.

The results of this study indicate that antazoline is an extremely effective anti-arrhythmic agent capable of abolishing atrial as well as ventricular premature systoles.

Abstract 7

Chlorothiazide Effects on Serum Lipids in Diabetic Patients. Sigmund R. Greenberg, M.D., Roy G. Klotz, Jr., M.D., and Paul M. Roediger, M.D. With the technical assistance of Carol M. Elkins, M.T. (ASCP), Abington Memorial Hospital, Abington, Pa.

The clinical aggravation of the diabetic state may be associated with elevations in serum lipids, especially neutral fats. Some diabetic patients on chlorothiazide therapy respond with a deterioration of their diabetic state as measured not only by hyperglycemia but also by serum lipids.

After one week of chlorothiazide therapy

(1500 mg. daily) in ten diabetic patients there were mean elevations of all serum lipids. However, statistical evaluation did not reveal significant mean elevations. However, within the group of the ten diabetic patients some responded with a marked neutral fat elevation (one patient's serum became turbid). Therefore, chlorothiazide may cause lipemia in diabetics who reveal a deterioration in their diabetic state. It is, at this time, impossible to predict which diabetic will react in this fashion.

In six control patients treated with chlorothiazide there were no mean elevations of lipids but a rise in the mean two hour post-glucose load blood sugar ($p < .05$). This was noted in spite of a normal mean fasting blood sugar level. As noted by prior investigators there was a mean uric acid elevation in the controls ($p < .05$).

Abstract 8

SYNDROME OF RUPTURED CHORDAE TENDINAE. Joseph F. Uricchio, M.D., and Henry T. Nichols, M.D., Department of Medicine, Hahnemann Medical College and Hospital.

The present report deals with the Syndrome of Ruptured Chordae Tendinae. It is based on a study of ten cases encountered out of a total of 250 undergoing open heart surgery for mitral stenosis and regurgitation during the time interval from November of 1959 until the present.

The normal anatomy of the mitral valve is reviewed. Two groups of chordae originate from the posterior papillary muscle and are attached to the posterior part of each leaflet respectively, and two from the anterior papillary muscle which attach to the anterior part of the leaflet. With rupture a flail valve is produced.

In terms of etiology, bacterial endocarditis has long been a major factor in the cause of ruptured chordae. Only one of our patients presented such a history. Another mentioned previous anterior chest wall injury, but the major mechanism in most patients appeared to be the edema associated with acute rheumatic inflammatory state.

In all patients the mitral valves were inspected at surgery. In half of the cases chordae arising from the posterior papillary muscle and attached to the posterolateral half of the anterior were involved.

The clinical syndrome is reviewed. The ages

The clinical syndrome was reviewed. The ages of the patients ranged from 28 to 53 and long asymptomatic intervals were common. Dyspnea and fatigue were common. All patients presented evidence for a rough pansystolic murmur at the apex on cardiac auscultation and in one it simulated the murmur of aortic stenosis. Marked cardiac enlargement on x-ray was present in only two patients. Massive enlargement of the left atrium was uncommon. The pulmonary artery was not prominent. In half of the cases the electrocardiogram revealed evidence of left ventricular hypertrophy and atrial fibrillation.

The survival treatment was discussed. All patients were operated on utilizing extracorporeal circulation. The mortality rate was 10%. Followup studies indicate that this type of surgery can correct this unusual form of mitral regurgitation.

Abstract 9

THE OCCURRENCE OF SERIOUS HEMORRHAGIC COMPLICATIONS OF ANTICOAGULANT THERAPY. Bernard H. Pastor, M.D., Myron E. Resnick, M.D., and Theodore Rodman, M.D., Medical Service, Veterans Administration Hospital, Philadelphia, Pa.

The widespread use of anticoagulants, particularly their application to the long-term management of non-hospitalized patients, has exposed an increasing number of people to the risk of hemorrhage. During the past few years we have encountered 15 cases of serious anticoagulant-induced hemorrhage, 3 of them fatal, which illustrate the disastrous consequences of failure to observe sound principles of anticoagulant therapy.

The frequency with which bleeding occurs will be influenced by a number of factors, including the conditions under which therapy must be managed, the selection of patients for

long-term therapy, the skill and experience of the physician managing the therapy, and the adequacy and reliability of laboratory control.

Bleeding will be more frequent in long-term ambulatory patients than in hospitalized patients with close supervision and frequent laboratory control. Since patient error is an important cause of trouble, the patient selected for long-term anticoagulant therapy should be intelligent, cooperative, and well informed as to the serious nature of this form of therapy and the risk of hemorrhage. He should have no complicating disease or hazardous occupation that would increase the risk of hemorrhage nor should he be taking ulcerogenic drugs or adrenocorticosteroids.

The physician must exercise care in the selection and instruction of patients, have a good working knowledge of the properties and dosages of the drugs used, make correct and adequate use of appropriate laboratory data and be alert for the development of hemorrhagic complications.

The importance of reliable laboratory control deserves emphasis, since the physician may be misled or given a false sense of security by a prothrombin time reported in the therapeutic range when the patient is actually at dangerous levels. While the occurrence of serious hemorrhage is most often related to severe hypoprothrombinemia, many patients have bleeding with the prothrombin time in the therapeutic range. In about one-third of the patients who bleed some underlying organic cause for hemorrhage may be found.

The most frequent hemorrhagic manifestations encountered are hematuria, ecchymosis, epistaxis, bleeding gums, hemoptysis and hematoma. The most common fatal complication is cerebral hemorrhage, but it is likely that the anticoagulants do not cause the hemorrhage but merely increase its seriousness and probability of a fatal outcome. The second largest number of fatalities is probably the result of gastrointestinal hemorrhage. A number of unusual sites of serious hemorrhage have been reported.

The risk of hemorrhage cannot be eliminated entirely, since bleeding is an extension of the therapeutic effect of anticoagulants. In experienced hands the incidence of bleeding varies from 10 per cent in hospitalized patients to as much as 50 per cent in long-term therapy of ambulatory patients. The incidence of serious hemorrhage varies from 2 per cent in short-term to 10 per cent in long-term therapy.

With careful medical supervision and adherence to the principles enumerated above the occurrence of serious or fatal hemorrhage can be kept to a minimum and need not constitute an important limitation to the use of this form of therapy when it is indicated.

Abstract 10

HYPOCALCEMIA AND HYPOPHOSPHATEMIA ACCOMPANYING OSTEOBLASTIC OSSEOUS METASTASES: STUDIES OF CALCIUM AND PHOSPHATE METABOLISM AND PARATHYROID FUNCTION. George D. Ludwig, M.D., Department of Medicine, University of Pennsylvania School of Medicine.

The medical literature contains few reports of hypocalcemia accompanying osteoblastic osseous metastases, and the combination of hypocalcemia and hypophosphatemia accompanying such lesions has not been described previously. Five patients displaying hypocalcemia in association with osteoblastic metastases form the substance of this report.

TABLE 1

	Diagnosis	Serum Ca mg/100 ml.	Serum P mg/100 ml.	Serum Phosphatase (SJR units)		Tetany
				Alk.	Acid	
W. T.	Carcinoma Prostate	5.3	1.5	106	5.4	Severe
M. H.	Carcinoma Prostate	7.9	1.5	44	0.7	0
L. K.	Carcinoma Prostate	7.4	3.1	30	1.6	Mild
J. McG.	Carcinoma Lung	7.4	2.3	27	—	0
R. S.	Carcinoma Breast	7.4	2.4	49	—	Mild

Two of the five patients, whose primary lesions were carcinoma of the prostate gland, also had marked hypophosphatemia, and, in both, estrogen therapy appeared to induce the

hypocalcemia and hypophosphatemia. A third patient having osteoblastic metastases from prostate carcinoma also developed hypocalcemia only after estrogenic therapy, but the serum phosphate remained normal. The other two patients, who were never given estrogens, developed less severe degrees of hypocalcemia and hypophosphatemia as a result of osteoblastic metastases from primary carcinoma of the breast and lung, respectively. One patient developed frank tetany, with serum calcium concentrations as low as 5 mg./100 ml., and two others displayed numbness, tingling, and positive Chvostek signs. Other causes of chemical osteomalacia, such as intestinal malabsorption, vitamin D-resistant rickets, and primary renal tubular disease, were excluded. A number of studies of calcium-phosphate metabolism and parathyroid function were performed in four of the five patients. These included an Ellsworth-Howard test, and the response to infusions of calcium and of buffered phosphate solutions. This enabled calculation of the percentage tubular reabsorption of phosphate (% TRP), theoretical renal phosphate threshold (Tm_p), ratio of phosphate clearance to creatinine clearance (C_p/C_{cr}), and skeletal retention of calcium. Hypocalcemia was accounted for by the great avidity of the skeleton for calcium. In addition, evidence suggesting the presence of secondary hyperparathyroidism was obtained.

It is postulated that the sequence of metabolic events is as follows: 1) Osteoblastic metastases cause increased deposition of calcium and phosphate in bone, tending to decrease serum concentrations of both ions; 2) Hypocalcemia is thereby induced, and this results in stimulation of the parathyroid glands; 3) Secondary hyperparathyroidism then causes a further decrease in serum phosphate concentration, ultimately, in some instances, to hypophosphatemic levels; 4) Treatment with estrogens, which are well known to enhance deposition of calcium and phosphate in bone, provokes the development of hypocalcemia or aggravates it if it is already present.

Abstract 11

THE USE OF THYROTROPIN IN THE ASSESSMENT OF THYROID FUNCTION. Bertram J. Channick, M.D., Department of Medicine, Temple University School of Medicine.

The determination of mild states of thyroid failure in the absence of definite alterations in laboratory tests has been a vexing problem. Patients are frequently encountered with symptoms and signs suggestive of hypothyroidism and in whom the serum protein bound iodine and thyroidal radioactive iodine uptake are low normal. Not uncommonly, these patients are taking thyroid hormone, thus invalidating the usual thyroid function studies. Jefferies (1) first proposed the term "low thyroid reserve" for those patients who have a normal basal thyroidal radioactive iodine uptake and serum protein bound iodine, but in whom no increase can be produced in these values following thyrotropin administration. Such patients are probably under maximal endogenous thyrotropin stimulation, suggesting a failure of the normal pituitary thyroidal feed-back relationship. This would indicate that the thyroid gland is hypofunctioning and that the normal serum protein bound iodine and radioactive iodine uptake values represent the maximal function of the gland.

In the present study all patients had a basal serum protein bound iodine and 24 hour thyroidal radioactive iodine uptake. A single injection of 20 units of Thyrotropin (Armour) was administered intramuscularly, and twenty four hours later a repeat serum protein bound iodine and thyroidal radioactive iodine uptake were done. Eight euthyroid patients had a mean increase of the serum protein bound iodine of 2.9 Mcgms.%, with a range of 1.5 Mcgms.% to 4.3 Mcgms.%. There was a mean increase of 15% in the thyroidal radioactive iodine uptake with a range of 5% to 70%. Thirteen patients with primary thyroidal myxedema had a mean change of zero in the serum protein bound iodine level, with a range of −0.5 Mcgms.% to 0.5 Mcgms.% 24 hours after the administration of a single intramuscular injection of 20 units of thyrotropin.

The mean increase in the 24 hour radioactive iodine uptake was 0.5%. In five patients with mild hypothyroidism there was a mean increase in the serum protein bound iodine of 0.6 Mcgms.%, with a range of −0.5 Mcgms.% to 1.3 Mcgms.%. There was a wide range of increase in the radioactive iodine uptake (1–15%). Following thyrotropin administration, there was an increase in the serum protein bound iodine level of 1.5 Mcgms.% or higher in all of six patients who had normal thyroid function and who were taking thyroid hormone. In one instance in this group, the radioactive iodine uptake only increased 3%. The remainder had an increase greater than 5%. The maximum increase of the serum protein bound iodine level in seven hypothyroid patients taking thyroid hormone was 1.2 Mcgms.% following thyrotropin administration. The maximum increase in the radioactive iodine uptake was 3%. In nine euthyroid patients taking inorganic iodide there was in every instance an increase of serum protein bound iodine levels of 1.5 Mcgms.% or higher after thyrotropin injection. There was no significant change in the radioactive iodine uptake. The maximum change among four hypothyroid patients taking inorganic iodide was 0.5 Mcgms.%, although the basal level was frequently markedly elevated.

It would appear that the determination of thyroid reserve function utilizing thyrotropin is a valuable means of assessing the degree of thyroid activity. An increase of less than 1.5 Mcgms.% in the serum protein bound iodine 24 hrs. after the administration of 20 units of thyrotropin would strongly indicate that hypothyroidism exists. Administration of thyroid hormone or iodine does not seem to interfere with the protein bound iodine response to thyrotropin, even though the basal level may be markedly elevated.

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Abstract 12

The Clinical Significance of Simultaneous Pleural and Venous Glucose Determination. James E. Clark, M.D., Department of Medicine, Jefferson Medical College of Philadelphia.

The glucose concentration in pleural fluid has been one of many analyses utilized in an attempt to guide the physician in diagnosis and treatment in patients with so called "idiopathic pleural effusions". Most observers have noted that the glucose level in tuberculous pleural effusions is low, giving various limits for diagnostic significance. A few observers in the English literature[1, 2], and more in the Italian literature[3, 4], have called attention to the difference which may exist between the glucose level of blood and the effusion at the time the thoracentesis is performed, but a minimum of emphasis was placed on the significance of these findings.

In the present study, 164 glucose determinations were performed in 47 patients with pleural effusions. Of these, 15 had tuberculosis, 11 had malignancy, 11 had cardiac failure, 7 had bacterial pneumonia, and 3 were associated with other diseases.

In each patient specimens were obtained simultaneously from the pleural effusion and venous blood and were placed directly into tubes containing oxylate, 5 mgm of thymol and 50 mgm of sodium fluoride. Glucose determinations were performed while the specimens were still warm. Repeated determinations were done in several patients, and in six, modified glucose tolerance tests were performed simultaneously in blood and pleural fluid. Other studies done on the effusions included culture for routine bacteriology, cultures for fungus and culture on Lowenstein-Jensen media, total and differential cell counts, quantitative protein and protein electrophoresis, specific gravity, and cell block for histology.

The findings showed that there was a significant lowering of the pleural glucose content in tuberculous effusions compared to a simultaneous blood level. Only half of the patients with nontuberculous pneumonia and

effusion had lower glucose levels in the effusion compared to blood, and in the patients with cardiac failure and malignancy, the only cases in which the glucose content of pleural fluid was less than blood was in diabetics, or if the pleura was greatly thickened. Glucose tolerance tests done simultaneously in pleural effusions and blood confirmed these findings. It is suggested that the glycolytic action of *M. tuberculosis* is less likely to be responsible for this phenomenon than the physical condition of the pleura due to its thickness and to its relative state of vascularity in the various diseases.

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List of College Lectures, 1961

4 January 1961

WITT, PETER N. Tranquilizers: Experimental Proof for their Specific Effects. (Nathan Lewis Hatfield Lecture XLV; *Transactions & Studies*, July 1961).

1 February 1961

BRAUER, RALPH W. Liver Circulation, Liver Function, and Liver Integrity. (Mary Scott Newbold Lecture LXXI; *Transactions & Studies*, October 1961).

21 February 1961

WRIGHT, ARTHUR DICKSON. The History of Opium. (Kate Hurd Mead Lecture XIII; *Transactions & Studies*, July 1961).

1 March 1961

ROWE, WALLACE P. Mouse Polyoma Virus Infection. (Mary Scott Newbold Lecture LXXII; *Transactions & Studies*, October 1961).

5 April 1961

MCKUSICK, VICTOR A. Heritable Disorders of Connective Tissue. (James M. Anders Lecture XL; *Transactions & Studies*, January 1962).

10 May 1961

Joint Meeting of the Philadelphia County Medical Society and the College of Physicians of Philadelphia.

I. Presentation of the 38th Annual Strittmatter Award of the Philadelphia County Medical Society to Dr. William N. Parkinson by Dr. Charles M. Thompson, Chairman, Award Committee.

II. Presentation of the Benjamin Rush Awards for the year 1961 to Mr. Bruce D. Smith, Founder of the Eastern Pennsylvania Chapter, Arthritis and Rheumatism Foundation, and Mrs. Arlene Dickler Grass, Heart Association of Southeastern Pennsylvania, by Dr. David A. Cooper, Chairman, Award Committee.

III. Presentation of citations to physicians who have completed fifty years in the practice of medicine. Citations awarded by Dr. Thomas W. McCreary, President, Medical Society of Pennsylvania.

4 October 1961

KETY, SEYMOUR S. Contributions of Biochemistry to Psychiatry. (Alvarenga Prize Lecture XXII; *Transactions & Studies, January 1962*).

1 November 1961

RUTSTEIN, DAVID D. Standards for Medical Practice. (James M. Anders Lecture XLI; *Transactions & Studies*, April 1962). (Joint Meeting of the College of Physicians of Philadelphia and the Philadelphia County Medical Society.)

21 November 1961

BURNEY, LEROY E. The Health Sciences: A Common Bond Among All Nations. (Arthur Parker Hitchens Lectures VI; *Transactions & Studies*, April 1962). (Joint Meeting of the College of Physicians of Philadelphia and the Pennsylvania Public Health Association, Region One.)

6 December 1961

BLUMBERG, JOE M. Laboratory Medicine in Russia. (Thomas Dent Mütter Lecture LXXIV; *Transactions & Studies*, July 1962).

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1959. Brady, Luther Weldon, Jr., Hahnemann Hospital, Broad & Race Sts. (2)
1954. Bralow, S. Philip, 3701 N. Broad St. (40)
1942. Branen, William T., Whitby & Cypress Aves., Yeadon, Pa.

1921. Bransfield, John W., 2031 Locust St. (3)
1948. Braun, William, 406 Cooper St., Camden, N. J.
1953. Brav, Solomon S., 5575 N. Park Ave. (41)
1953. Breckenridge, Robert L., Our Lady of Lourdes Hosp., 1600 Haddon Ave., Camden 3, N. J.
1961. Breslow, Irwin H., 419 S. 19th St. (46)
1946. Briscoe, Clarence Conway, 811 Spruce St. (7)
1953. Brobeck, John R., Univ. of Pa. School of Medicine (4)
1958. Brody, Henry, Einstein Medical Center, York & Tabor Rds. (41)
1952. Brody, Morris W., 1930 Chestnut St. (3)
1948. Brogan, Edmund J., Thomas Wynne Apartment, Wynnewood, Pa.
1953. Brooke, John A., 1431 Spruce St. (2)
1958. Brooks, Frank P., Hospital of the Univ. of Pa. (4)
1936. Brown, Clark E., Lancaster Ave. & City Line Ave. (51)
1932. Brown, Claude P., 1930 Chestnut St. (3)
1959. Browneller, Ellsworth R., Jefferson Hospital (39)
1961. Brunt, Manly Y., 111 N. 49th St. (39)
1939. Brust, Raymond M., 4710 Chester Ave. (43)
1953. Bucher, Robert M., 3401 N. Broad St. (40)
1961. Buerk, Minerva S., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1952. Bumgardner, Heath D., 3701 N. Broad St. (40)
1940. Burnett, W. Emory, 3401 N. Broad St. (40)
1954. Burros, Harry M., 419 S. 19th St. (46)
1941. Butler, Miriam, Watersmeet, Glen Mills, Pa.
1957. Calhoun, John Alfred, Jr., 214 Elm Ave., Swarthmore, Pa.
1958. Cameron, Charles S., 235 N. 15th St. (2)
1928. Campbell, Edward H., 133 S. 36th St. (4)
1952. Campbell, Edward W., Abington Memorial Hospital
1944. Campion, Richard J., Box 136 Springhouse, Ambler, Pa.
1960. Cancelmo, John B., 5012 Spruce St. (39)
1931. Cantarow, Abraham, 1025 Walnut St. (7)
1952. Cardone, John B., 831 N. 63rd St. (31)
1935. Carey, Lawrence S., 330 S. 9th St. (7)
1931. Cariss, Walter L., 51 N. 39th St. (4)
1956. Carnwath, John Wallace, Summit & Highland Aves., Jenkintown, Pa.
1930. Carpenter, Chapin, 1930 Chestnut St. (3)
1959. Carrington, Elsie R., Woman's Medical College (29)
1960. Carroll, Robert T., 1015 Sansom St. (7)
1917. Carson, John B., Newton Square, Pa.
1956. Carty, James Byron, 51 Hampden Rd., Upper Darby, Pa.
1956. Casey, Paul R., 8350 Roosevelt Blvd. (15)
1937. Castallo, Mario A., 1621 Spruce St. (3)
1943. Castigliano, S. Gordon, 853 Mt. Pleasant Rd., Bryn Mawr, Pa.
1949. Caswell, H. Taylor, 3401 N. Broad St. (40)
1954. Catenacci, Alfred J., 1417 S. Broad St. (47)
1954. Cathcart, Richard T., 739 S. Broad St. (47)
1957. Cattie, Vincent J., The Benson, E. 207A., Jenkintown, Pa.
1950. Chamberlain, Richard H., 3400 Spruce St. (4)
1939. Chamberlin, George W., Reading Hospital, Reading, Pa.
1900. Chance, Burton, 9 Llanalew Road, Haverford, Pa.
1945. Chance, Burton, Jr., 8236 Germantown Ave. (18)
1958. Channick, Bertram J., 3701 N. Broad St. (40)
1954. Charny, Charles W., 2039 Delancey Pl. (3)
1960. Chirico, Anna-Marie, Hosp. of Univ. of Pa. (4)

1947. Chouké, Kehar S., P. O. Box 5447, Kecoughtan Station, Hampton, Va.
1945. Cianfrani, Theodore, 1930 Chestnut St. (3)
1939. Ciccone, Emmet F., 2021 Murray St. (15)
1960. Cinquino, Mario A., 1518 S. Broad St. (46)
1960. Clader, Stanley C., 825-A Glenbrook Ave., Bryn Mawr, Pa.
1951. Clagett, Augustus H., Jr., 1618 N. Broom St., Wilmington 6, Del.
1929. Clark, Eliot R., 315 S. 41st St. (4)
1951. Clark, John K., 36th & Spruce Sts. (4)
1947. Clark, Thomas Williams, 218 W. Chestnut Hill Ave. (18)
1947. Classen, Charles H., Cushman Rd. and Lancaster Ave., Rosemont, Pa.
1958. Closson, Edward W., 2320 S. Broad St. (45)
1910. Cloud, J. Howard, 111 St. Pauls Road, Ardmore, Pa.
1949. Cohen, Louis B., 1320 Arrott St. (24)
1953. Cohen, Robert V., 520 Spring Ave., Elkins Park 17, Pa.
1934. Collins, Leon Howard, Jr., 133 S. 35th St. (4)
1943. Colonna, Paul C., 133 S. 36th St. (4)
1949. Conger, Kyril B., 3401 N. Broad St. (40)
1961. Coon, Juluis M., 1025 Walnut St. (7)
1945. Coonel, Pauline, 47 E. Mt. Pleasant Ave. (19)
1930. Cooper, David A., 1520 Spruce St. (2)
1953. Cooper, Donald R., Woman's Medical College, 3300 Henry Ave. (29)
1960. Cooper, Edward Sawyer, 6710 Lincoln Dirve (19)
1947. Coppolino, John F., 1807 S. Broad St. (45)
1952. Corbit, John D., Jr., 3717 Chestnut St. (4)
1959. Cormeny, George F., 3818 Chestnut St. (4)
1941. Cornelius, Chalmers E., 119 Summit Ave., Jenkintown, Pa.
1911. Cornell, Walter S., Board of Public Education, Parkway and 21st St. (3)
1914. Corson, Edward F., 136 S. 16th St. (2)
1946. Costello, Thomas J., 825 Glenbrook Ave., Bryn Mawr, Pa.
1924. Cowan, Alfred, 1930 Chestnut St. (3)
1940. Cowan, Thomas H., 1930 Chestnut St. (3)
1907. Crampton, George S., 2031 Locust St. (3)
1947. Crane, A. Reynolds, 807 Spruce St. (7)
1937. Crane, Martin P., 4701 Pine St. (43)
1952. Crellin, J. Antrim, 1930 Chestnut St. (3)
1955. Crist, Walter A., 211 N. 5th St., Camden, N. J.
1921. Crossan, Edward T., Buttonwood Hall, Conshohocken, Pa.
1937. Crump, Jean, R. D. 2, West Chester, Pa.
1959. Cullen, Milton L., 1321 W. Tabor Rd. (41)
1934. Custer, R. Philip, 643 Moreno Road, Narberth, Pa.
1958. D'Alonzo, Walter A., 1647 S. 15th St. (45)
1938. Dannenberg, Arthur M., Sr., 235 S. 15th St. (2)
1950. Dannenberg, Arthur M., Jr., Henry Phipps Institute, Univ. of Pa. (4)
1951. Daugherty, Earl A., 2818 W. Girard Ave. (30)
1953. Davie, John H., 37 S. 20th St. (3)
1947. Davis, C. Nelson, Malvern Institute, Malvern, Pa.
1936. Davis, David M., 208 Haverford Sq. Bldg., Haverford, Pa.
1957. Davis, John Evan, Tedwyn Apts., 840 Montgomery Ave., Bryn Mawr, Pa.
1951. Davis, J. Wallace, 135 S. 18th St. (3)
1937. Davis, Perk Lee, P. O. Box 701, Paoli, Pa.
1961. Dawber, Bryan A., Penn Mutual Life Insurance Co. (5)
1935. Deaver, J. Montgomery, Lankenau Medical Bldg. (51)

1957. Decker, John Paul, Pennsylvania Hospital (7)
1957. Dees-Porch, Frances, Glendale Road & Chestnut Sts., Upper Darby, Pa.
1947. Deihne, Theodore L., Adams Avenue and Roosevelt Blvd. (24)
1935. Deibert, Irvin Elmer, 538 Cooper St., Camden, N. J.
1958. Deitz, George W. III, 1146 Arrott St. (24)
1955. De Long, Samuel L., 860 Lancaster Ave., Bryn Mawr, Pa.
1952. DeLuca, Charles Q., 255 S. 17th St. (3)
1952. De Orsay, Ralph H., 1241 Lindale Ave., Drexel Hill, Pa.
1951. De Palma, Anthony F., 248 S. 21st St. (3)
1959. DeTuerk, John J., 1930 Chestnut St. (3)
1928. Dewees, A. Lovett, Glen Mills, Del. Co., Pa.
1959. Dickens, Helen O., 1512 W. Oxford St. (21)
1958. Dickstein, Benjamin, 6810 Castor (24)
1956. Dietrich, Herbert James, Jr., 1830 Delancey Place (3)
1952. Diglio, Victor A., 2200 St. James Place (17)
1960. Dinon, Louis R., 330 S. 9th St. (7)
1920. Doane, Joseph C., 617 W. Hortter St. (19)
1948. Dohan, Francis Curtis, 80 Princeton Road, Cynwyd, Pa.
1954. Donaldson, James B., 1901 Walnut St. (3)
1946. Donnelly, Andrew J., 33rd and Powelton Ave. (4)
1933. Donnelly, Joseph C., 6832 Ogontz Ave. (38)
1937. Donnelly, Robert T. M., 5205 N. Broad St. (41)
1954. Downing, Daniel F., 8864 Norwood Ave. (18)
1952. Drayer, Calvin S., 111 N. 49th St. (39)
1949. Dripps, Robert D., 3400 Spruce St. (4)
1956. Dubin, Isadore N., Woman's Medical College (29)
1944. Dublin, George J., 1930 Chestnut St. (3)
1944. Dugger, John H., Episcopal Hospital (25)
1935. Duncan, Garfield G., 330 S. 9th St. (7)
1951. Dunne, Francis S., 133 S. 36th St. (4)
1953. Dupler, Donald A., 4028 Walnut St. (4)
1942. Durant, Thomas M., 3401 N. Broad St. (40)
1947. Durkin, John Keenan, 49 Woodcroft Rd., Havertown, Pa.
1942. Dyer, W. Wallace, Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1936. Easby, Mary Hoskins, R. D. 1, Burlington, Vt.
1948. Eaton, Francis H., 4007 Chestnut St. (39)
1937. Edeiken, Joseph, 2130 Delancey Pl. (3)
1944. Eger, Sherman A., 255 S. 17th St. (3)
1944. Erhich, William E., 540 W. Hortter St. (19)
1956. Eiman, John W., Abington Memorial Hospital, Abington, Pa.
1959. Eisenhower, James S. D., Jr., 2704 Pacific Ave., Wildwood, N. J.
1958. Eisman, Sylvan H., 3600 Spruce St. (4)
1946. Elfman, Louis Kenneth, 6330 Lebanon Avenue (31)
1959. Elias, Elmer J., 474 Greenwood Ave., Trenton, N. J.
1949. Elkinton, J. Russell, Oak Lane, Moylan, Pa.
1961. Elliott, Frank A., 807 Spruce St. (7)
1957. Ellis, Richard A., 1711 Rittenhouse Square (3)
1955. Ellis, Samuel, 541 S. 46th St. (43)
1939. Ellis, Van Mashburn, 1528 Spruce St. (2)
1928. Ellison, Richard T., 8601 Stenton Ave. (18)
1936. Ellson, J. Vernon, Glendale Road & Chestnut St., Upper Darby, Pa.
1937. Elsom, Kendall A., Scott Paper Co. (13)

1934. Ely, William C., 3912 Chestnut St. (4)
1932. Engel, Gilson C., Lankenau Medical Bldg. (51)
1945. English, O. Spurgeon, 3401 N. Broad St. (40)
1942. Erb, William H,, 133 S. 36th St. (4)
1957. Erdman, William James, II, 3400 Spruce St. (4)
1950. Ersner, Matthew S., 1915 Spruce St. (3)
1957. Etzl, Michael M., 9025 Frankford Ave. (14)
1954. Evans, William W., Box 2, Bryn Mawr, Pa.
1948. Everts, Glenn S. 5515 Wissahickon Ave., Apt. D-403 (44)
1955. Eynon, Harold K., Route 70 at East Gate, Barclay Farm, Haddonfield, N. J.
1946. Farell, David M., 1912 Spruce St. (3)
1903. Farr, Clifford B., Railroad Ave. & County Line Rd., Bryn Mawr, Pa.
1945. Farrar, George Elbert, Jr., 528 Scott Rd., Gladwyne, Pa.
1953. Farrell, Harry L., 1930 Chestnut St. (3)
1930. Farrell, John T., Jr., 255 S. 17th St. (3)
1935. Ferguson, Lewis Kraeer, 419 S. 19th St. (46)
1936. Fetter, Ferdinand, 322 S. 21st St. (3)
1945. Fetter, John S., 842 Worrell Rd., Jenkintown, Pa.
1935. Fetter, Theodore R., 255 S. 17th St. (3)
1924. Fewell, Alexander G., 1924 Pine St. (3)
1952. Fields, Harry, 133 S. 36th St. (4)
1959. Fineberg, Charles, 255 S. 17th St. (3)
1955. Finestone, Albert J., 2039 Pine St. (3)
1960. Finkbiner, Rodman B., 811 Spruce St. (7)
1943. Finkelstein, K. Arthur, Graduate Hospital (46)
1955. Finkelstein, David, 419 S. 19th St. (46)
1955. Finley, John K., 527 Welsh St., Chester, Pa.
1954. Finn, Joseph L., 8014 Burholme Ave. (11)
1947. First, Arthur, 1714 Spruce St. (3)
1960. First, Howard E., 1714 Spruce St. (3)
1954. Fischer, Carl C. Girard College (21)
1950. Fischer, H. Keith, 100 W. Coulter St. (44)
1958. Fisher, Robert M., 118 Airdale Rd., Rosemont, Pa.
1956. Fite, Franklin K., Germantown Hospital (44)
1952. Fitts, William T., Jr., 3400 Spruce St. (4)
1928. Fitz-Hugh, Thomas, Jr., 2016 Delancey Pl. (3)
1952. Flexner, Louis B., 248 Anatomy-Chemistry Bldg., Univ. of Pa.
1928. Flick, John B., 819 Black Rock Rd., Gladwyne, Pa.
1954. Flick, John B., Jr., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1952. Flinn, Lewis B., 503 Delaware Ave., Wilmington, Del.
1939. Flippin, Harrison F., Lankenau Hospital (51)
1957. Forman, Simon B., 255 S. 17th St. (3)
1957. Fornwalt, George R., Brandon Road & Ludlow St., Upper Darby, Pa.
1954. Forster, H. Walter, Jr., 37 S. 20th St. (3)
1960. Foulger, John H., 601 Rockwood Rd., Wilmington (2) Del.
1941. Fox, C. Calvin, 1806 Spruce St. (3)
1957. Frankel, Donald S., 255 S. 17th St. (3)
1959. Frankel, Kalman, 111 N. 49th St. (39)
1955. Frayer, William C., 37 S. 20th St. (3)
1941. Frazier, William Doane, 419 Gilpin Rd., Narberth, Pa.
1952. Freed, Herbert, 255 S. 17th St. (3)
1956. Freeman, Joseph T., 8-A Rittenhouse Plaza (3)

1958. Freiwald, Milton J., 1530 Spruce St. (2)
1953. Fried, Paul H., 1812 Spruce St. (3)
1955. Friedenberg, Zachary B., 133 S. 36th St. (4)
1951. Friedman, Paul Sigmund, 1422 Chestnut St. (2)
1960. Friedmann, Sidney, 1740 Bainbridge St. (46)
1958. Frisch, Frederick, 888 Glenbrook Ave., Bryn Mawr, Pa.
1933. Fritch, James Scott, 269 S. 19th St. (3)
1937. Fritz, Herbert H., Pennswood Rd., Bryn Mawr, Pa.
1961. Frobese, Alfred S., 419 S. 19th St. (46)
1953. Fruchter, Joseph M., 2200 Benjamin Franklin Parkway, Park Towne, North (30)
1940. Fry, Kenneth E., 1719 Rittenhouse Sq. (3)
1935. Fry, Wilfred Eyles, 1930 Chestnut St. (3)
1937. Furlong, Thomas F., Jr., Times Medical Building, Ardmore, Pa.
1954. Gambescia, Joseph M., 1422 Race St. (2)
1935. Gammon, Geo. D., Univ. of Pa. Hospital (4)
1951. Garlichs, Richard W., 216 N. Monoa Road, Havertown, Pa.
1931. Garner, Vaughn C., Germantown Professional Building (44)
1953. Garnet, James D., 807 Spruce St. (7)
1959. Gartland, John J., 269 S. 19th St. (3)
1950. Garvin, Eugene J., 533 S. 46th St. (43)
1953. Geckeler, Edwin O., 269 S. 19th St. (3)
1952. Gefter, William I., 1900 Rittenhouse Square (3)
1935. Geist, Donald C., 301 E. City Line, Bala-Cynwyd, Pa.
1955. Gelfand, David, 1722 Pine St. (3)
1954. German, George B., 429 Cooper St., Camden, N. J.
1941. Gershon-Cohen, J., 255 S. 17th St. (3)
1959. Gerson, Irvin M., 1561 E. Tulpehocken St. (38)
1955. Gettes, Bernard C., 128 Overhill Rd., Cynwyd, Pa.
1934. Gibbon, John H., Jr., 1025 Walnut St. (7)
1939. Gibson, Glen Gregory, 2031 Locust St. (3)
1944. Gifford, Edward S., Jr., 1913 Spruce St. (3)
1956. Gilbert, Philip D., Cooper Hospital, Camden, N. J.
1947. Giletto, Basil J., 2020 Locust St. (3)
1940. Gill, A. Bruce, 1603 Normandy Drive, Mt. Dora, Fla.
1955. Gill, Robert J., 801 Spruce St. (7)
1922. Gilmour, William R., 6616 Woodland Ave. (42)
1952. Gilpin, Sherman F., Jr., 1023 Buery Building, 3701 N. Broad St.
1949. Ginsburg, Isadore W., 3401 N. Broad St. (40)
1958. Girsh, Leonard S., 3701 N. Broad St. (40)
1954. Gislason, Gerhard J., 136 S. 16th St. (2)
1956. Goldberg, Harry, 7913 Rolling Green Rd., Cheltenham, Pa.
1933. Goldburgh, Harold L., 1932 Spruce St. (3)
1958. Golub, Leib J., 136 S. 16th St. (2)
1949. Gopadze, Illarion I., 255 S. 17th St. (3)
1956. Goracci, Armando F., 2040 Poplar St. (30)
1937. Gordon, William, 5345 Spruce St. (39)
1956. Gouley, Benjamin, 5577 N. Park Ave. (41)
1957. Grahn, Henry Victor, 5132 Chester Ave. (43)
1926. Grant, Francis Clark, 750 Germantown Pike, Lafayette Hill, Pa.
1958. Greco, Toby A., 2506 S. 20th St. (45)
1940. Greene, Llyod B., 803 Spruce St. (7)
1952. Greening, Roy R., Dept. of Radiology, Jefferson Hospital (7)

1958. Greenspan, Benjamin, 1319 W. Tabor Rd. (41)
1955. Greenstein, Raphael H., 1710 Pine St. (3)
1934. Griffith, John Q., Jr., 6 N. Fredericksburg Ave., Margate, N. J.
1941. Groff, Robert A., Univ. of Pa. Hospital (4)
1952. Grotzinger, Paul J., 2121 Valley Rd., Huntingdon Valley, Pa.
1952. Grove, D. Dwight, 230 N. Broad St. (2)
1945. György, Paul, Univ. of Pa. School of Medicine (4)
1935. Hadden, Samuel B., 250 S. 18th St. (3)
1951. Hafkenschiel, Joseph H., Jr., 13 St. Asaph Rd., Bala-Cynwyd, Pa.
1945. Hahn, George A., 255 S. 17th St. (3)
1955. Hallahan, John D., 104 W. Front St., Media, Pa.
1951. Hallett, Joseph W., 136 S. 16th St. (2)
1961. Hammett, Van Buren O., 111 N. 49th St. (39)
1959. Hampton, Louis J., 1025 Walnut St. (7)
1954. Hand, B. Marvin, 210 N. 15th St. (2)
1938. Hand, John G., 1724 Pine St. (3)
1947. Hanes, William James, 218 E. Beechtree Lane, Wayne, Pa.
1958. Hanlon, John J., 519 City Hall Annex (7)
1950. Hansen, A. Victor, 3401 N. Broad St. (40)
1957. Harasym, Emil L., 952 N. Franklin St. (23)
1956. Harbert, Frederick, Jefferson Hospital (7)
1952. Harer, W. Benson, State Rd. & Rogers Ave., Bywood, Pa.
1951. Harkins, Herbert P., 1930 Chestnut St. (3)
1959. Harris, James S. C., 5401 Wayne Ave. (44)
1932. Harris, Stanley E., 229 Maple Ave., Delnaco, N. J.
1948. Harris, T. N., 5112 Woodbine Ave. (31)
1929. Harrison, Francis G., 1900 Spruce St. (3)
1926. Hartmann, Fred I., 1914 Pine St. (3)
1946. Harvey, Edith E., 406 York Rd., Jenkintown, Pa.
1947. Harvey, Rolfe Marsh, 669 Mill Rd., Villanova, Pa.
1961. Harvie, Fred H., 3400 Spruce St. (4)
1935. Haskell, Benjamin F., 1427 Spruce St. (2)
1958. Haupt, George J., 1012 Walnut St. (7)
1960. Hausman, David H., Pennsylvania Hospital, 8th & Spruce Sts. (7)
1947. Havens, Walter Paul, Jr., 139 Cheswold Lane, Haverford, Pa.
1952. Hayllar, Benjamin L., 803 Spruce St. (7)
1961. Hayward, Malcolm L., 111 N. 49th St. (39)
1961. Heath, Frederick K., Merck, Sharp and Dohme, West Point, Pa.
1957. Hedges, Thomas R., Jr., 1711 Rittenhouse St. (3)
1961. Heggestad, Gilman E., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1953. Henny, George C., 3400 N. Broad St. (40)
1944. Herbut, Peter A., Dept. of Pathology, Jefferson Medical College Hospital (7)
1954. Herron, James R., 1486 Haddon Ave., Camden 3, N. J.
1957. Hess, Catherine B., 338 Gowan Ave. (19)
1949. Heyl, W. Meredith, 100 W. Coulter St. (44)
1956. Hildreth, Eugene A., University of Penna. Hospital (4)
1961. Hilferty, Daniel J., Jr., Wildman Arms Apts., Lansdowne, Pa.
1952. Hinkson, DeHaven, 329 N. 40th St. (4)
1924. Hirst, John C., 2d., 500 N. 20th St. (30)
1943. Hitschler, William J., Bethlehem Pike & Summit (18)
1944. Hneleski, Ignatius S., 802 S. 48th St. (43)
1943. Hockaday, Agnes, 316 Shadeland Ave., Drexel Hill, Pa.

1939. Hodes, Philip J., Dept. of Radiology, Jefferson Medical College (7)
1947. Hodges, John H., 1025 Walnut St. (7)
1959. Hoffman, Francis H., 3401 N. Broad St. (40)
1948. Hoffman, George L., Jr., 133 S. 36th St. (4)
1954. Hollander, George, 3500 Vista St. (36)
1949. Hollander, Joseph L., 36th & Spruce Sts. (4)
1951. Hollis, Charles B., 28 W. School Lane (44)
1952. Holloway, Edward E., 1736 Pine St. (3)
1949. Hopkins, Henry U., Garden Court Apts., 47th & Pine Sts. (43)
1953. Horan, Charles A., 734 N. 63rd St. (31)
1946. Horan, Gerald W., 5819 Chester Ave. (43)
1947. Horwitz, Orville, Hospital of University of Pa. (4)
1950. Houlihan, Carl T., 207 McClatchy Bldg., Upper Darby, Pa.
1944. Houlsel, Edmund L., 255 S. 17th St. (3)
1928. Houser, Karl Musser, 2035 Delancey Pl. (3)
1958. Howard, John M., 230 N. Broad St. (2)
1948. Howland, Alvin Wilcox, 255 S. 17th St. (3)
1946. Howson, John Yeatts, 316 Lancaster Ave., Wayne, Pa.
1951. Hubbard, John P., University of Penna. School of Medicine (4)
1947. Huber, John Franklin, Temple University School of Medicine (40)
1937. Hughes, Joseph, 111 N. 49th St. (39)
1939. Hughes, P. Boland, 419 Hillbrook Rd., Bryn Mawr, Pa.
1951. Hundley, J. Warren, 3818 Chestnut St. (4)
1954. Hunsicker, William C., Jr., 255 S. 17th St. (3)
1946. Hunt, William T., Jr., 6 Penn Center Plaza (3)
1921. Hunter, Robert John, 928 N. 63rd St. (31)
1952. Hyman, Harold L., 3401 N. Broad St. (40)
1950. Imbriglia, Joseph E., 329 Shadeland Ave., Drexel Hill, Pa.
1949. Ingraham, Norman R., Jr., Stenton and Whitemarsh Aves. (18)
1957. Isaacson, Howard, Haverford Ave. & Drexel Rd.
1951. Isard, Harold J., Mt. Sinai Hospital, 5th & Reed Sts. (47)
1951. Israel, Harold L., 304 S. 19th St. (3)
1947. Israel, S. Leon, 807 Spruce St. (7)
1947. Jaeger, Rudolph, Jefferson Medical College Hospital (7)
1941. Jeffers, William A., 503 Owen Road, Wynnewood, Pa.
1960. Jenson, William K., 330 S. 9th St. (7)
1943. Johnson, Julian, 3400 Spruce St. (4)
1959. Johnson, Robert G., 1012 Walnut St. (7)
1938. Johnson, Thomas A., 135 S. 18th St. (3)
1952. Jonas, Karl C., 2601 Parkway (30)
1957. Jordan, Luke W., 1486 Haddon Ave., Camden 3, N. J.
1961. Joyner, Claude R., Jr., 3400 Spruce St. (4)
1957. Kacher, Leon, 2037 Pine St. (3)
1957. Kane, Sydney H., 3458 Cottman Ave. (49)
1948. Kaplan, Louis, 2040 Pine St. (3)
1938. Kasper, Kelvin A., 135 S. 18th St. (3)
1958. Kasser, Max D., 37 S. 20th St. (3)
1945. Katz, G. Henry, 111 N. 49th St. (39)
1958. Katz, Jacob, 136 S. 16th St. (2)
1941. Kauffman, M. Luther, Medical Arts Bldg., Jenkintown, Pa.
1947. Kay, Calvin Frederick, Univ. of Pa. Hospital (4)
1954. Kaye, Robert, Children's Hospital, 1740 Bainbridge St. (46)

1947. Keefer, George Pfahler, 136 S. 16th St. (2)
1949. Keiserman, Joseph, 5460 Baltimore Ave. (43)
1959. Keitel, Hans G., 1025 Walnut St. (7)
1932. Kelly, Herbert T., 1900 Spruce St. (3)
1961. Kelly, William E., 111 N. 49th St. (39)
1941. Kennedy, Patrick J., 32 Hampden Rd., Upper Darby, Pa.
1948. Kern, Franklin Moore, 903 Nicholson Rd., Wynnewood, Pa.
1921. Kern, Richard A., Temple University Hospital, 3401 N. Broad St. (40)
1935. Keyes, Baldwin L., 2031 Locust St. (3)
1960. Kimmich, John M., Campbell Company, Camden, N. J.
1936. King, Orville C., 330 S. 9th St. (7)
1958. Kirby, Charles K., 3400 Spruce St. (4)
1952. Kirshner, Jacob J., 1930 Chestnut St. (3)
1960. Kitchell, J. Roderick, 3719 Chestnut St. (4)
1920. Klauder, Joseph V., 1934 Spruce St. (3)
1920. Klein, Thomas, 250 S. 18th St. (3)
1952. Kleinbart, Morris, 1922 Pine St. (3)
1954. Kligman, Albert M., 36th & Spruce Sts. (4)
1934. Kline, Oram R., 514 Cooper St., Camden, N. J.
1959. Kline, Oram R., Jr., 524 Cooper St., Camden, N. J.
1948. Klingensmith, Paul O., Med. Science Bldg., Lankenau Hosp. (51)
1958. Klingensmith, Walter C., 3600 Spruce St. (4)
1956. Klinghoffer, June F., Woman's Medical College (29)
1932. Klopp, John W., Gwynedd Valley, Pa.
1960. Knopf, Carl L., 5312 Spruce St. (39)
1960. Knorr, John K., 3rd., Lankenau Medical Bldg. (51)
1959. Knowles, Harry J., 255 S. 17th St. (3)
1945. Kobler, H. B., 658 N. 63rd St. (31)
1959. Koiwai, Eichi Karl, 235 N. 15th St. (2)
1914. Kolmer, John A., Cynwyd, Pa.
1957. Koltes, John A., Jefferson Hospital, 14th Annex, 10th & Sansom Sts. (7)
1936. Konzelmann, Frank Williamson, Shore Memorial Hosp., Somer's Point, N. J.
1949. Koop, C. Everett, 1740 Bainbridge St. (46)
1952. Kornblueh, Igho H., Welsh Rd., & Verree Rd. (15)
1958. Kovach, Coleman W., 2031 Locust St. (3)
1941. Krall, J. Thomas, 85 N. Lansdowne Ave., Lansdowne, Pa.
1948. Kramer, David W., 2007 Pine St. (3)
1954. Krasnoff, Sidney O., Tabor Medical Bldg., York & Tabor Roads (41)
1944. Krauss, Frederick Harold, 136 S. 16th St. (2)
1952. Kravitz, Charles H., 626 Ashbourne Rd., Elkins Park, Pa.
1949. Kressler, Robert J., 330 S. 9th St. (7)
1941. Krewson, William E., 3rd, 1930 Chestnut St. (3)
1914. Krumbhaar, Edward B., P. O. Box 4056 (18)
1947. Kuhlenbeck, Hartwig, Woman's Medical College, 3300 Henry Ave. (29)
1947. La Boccetta, Alfred Charles, Phila. General Hospital, 34th St. & Curie Ave. (4)
1952. Lachman, John W., 3401 N. Broad St. (40)
1949. La Clair, Charles H., Jr., 1021 W. Main St., Norristown, Pa.
1951. Lame, Edwin L., 51 N. 39th St. (4)
1950. Lamont, Austin, 3400 Spruce St. (4)
1946. Lampe William T. 4207 Tyson Ave. (35)
1952. Lang, Warren R., 1012 Walnut St. (7)
1941. Langner, Paul H., Jr., 1208 Edmonds Ave., Drexel Hill, Pa.

1945. Lansbury, John, 3401 N. Broad St. (40)
1926. Laws, George M., 1907 Spruce St. (3)
1936. Leaman, William G., Jr., Presidential Apts: Adams House B-909 (31)
1950. Learner, Norman, 3701 N. Broad St. (40)
1920. Leavitt, Frederic Headley, 1527 Pine St. (2)
1957. Lee, Charles Trumbull, Jr., 33 E. Chestnut Hill Ave. (18)
1941. Leberman, Paul R., 136 S. 16th St. (2)
1942. Lehman, James A., The Stafford House, Chelten & Wissahickon Ave. (44)
1952. Lehman, J. Stauffer, 230 N. Broad St. (2)
1961. Leibfried, Jane M., 5501 Greene St. (44)
1960. Leiter, Samuel S., 1301 Westbury Drive, Overbrook Park (31)
1951. Leivy, Frank E., 255 S. 17th St. (3)
1944. Lell, William A., 333 S. 18th St. (3)
1935. Lemmon, William T., 133 S. 36th St. (4)
1943. Leopold, Irving H., 1711 Rittenhouse Sq. (3)
1955. Leopold, Robert L., 269 S. 19th St. (3)
1944. Lettiere, Anthony J., 425 E. State St., Trenton, N. J.
1933. Levering, J. Walter, Abington Memorial Hospital, Abington, Pa.
1959. Levick, Leonard J., 1300 E. Cliveden St. (19)
1958. Levine, Samuel, 7100 N. 19th St. (38)
1958. LeWinn, Edward B., Wyncote, Pa.
1960. Lewis, David H., Philadelphia General Hosp. (4)
1915. Lewis, Fielding O., Providence Road, Media, Pa.
1960. Lewis, George C., Jr., 133 36th St. (4)
1955. Lieberman, George E., 2019 Pine St. (3)
1956. Likoff, William, 249 N. Broad St. (2)
1940. Limberger, William A., 301 S. Church St., West Chester, Pa.
1958. Lin, David Y. P., 2228 S. Broad St. (45)
1938. Lindauer, M. August, 133 S. 36th St. (4)
1956. Lindquist, John N., 422 Sabine Ave., Wynnewood, Pa.
1927. Lindsey, Walter H., 325 Callowhill St., Perkasie, Pa.
1936. Lintgen, Charles, 1930 Chestnut St. (3)
1958. Lipschutz, Arthur, 7974 Fayette St. (19)
1959. Lipschutz, Herbert, 255 S. 17th St. (3)
1953. Lipsius, Edward I., 319 S. 16th St. (3)
1945. Lisker, Samuel, 255 S. 17th St. (3)
1959. Little, Ralph B., 111 N. 49th St. (39)
1944. Livezey, Mary M., 133 S. 36th St. (4)
1936. Llewellyn, Thomas H., 910 N. 63rd St. (31)
1907. Lodholz, Edward, The Fairfax, 43rd & Locust Sts. (4)
1951. Long, Joseph P., 1930 Chestnut St. (3)
1935. Long, William L., 2038 Locust St. (3)
1931. Longaker, Edwin P., 41 E. Montgomery Ave., Ardmore, Pa.
1951. Lorber, Stanley H., 3701 N. Broad St. (40)
1961. Lorry, Ralph W., 1247 E. Luzerne St. (24)
1960. Lovett, B. Frank, 300 Broadway, Camden, N. J.
1936. Lucchesi, Pascal Francis, 601 E. Gorgas Lane (19)
1960. Lucine, Albert A., 345 S. 19th St. (3)
1932. Lukens, Francis D. W., Univ., of Pa. Hospital (4)
1939. Luongo, Romeo A., 2054 Locust St. (3)
1947. Lurie, Max B., Henry Phipps Institute, Univ. of Pa. (4)
1951. Luscombe, Herbert A., 136 S. 16th St. (2)

1952. Lutman, Frank C., 100 W. Coulter St. (44)
1950. Lynch, J. Edward, 23 E. Wynnewood Rd., Wynnewood, Pa.
1953. Lyons, John W., 255 S. 17th St. (3)
1952. McCabe, Edward S., 136 S. 16th St. (2)
1932. McCahey, James F., Rittenhouse-Claridge, 18th & Walnut Sts. (3)
1958. McClenahan, John L., 39 E. Chestnut Hill Ave. (18)
1935. McClenahan, William U., 33 East Chestnut Hill Ave., Chestnut Hill (18)
1953. McCloskey, Joseph F., Jefferson Hospital. (7)
1955. McClure, Carroll R., 17 S. Church St., W. Chester, Pa.
1957. McConnell, Edward L., Jr., 2342 S. Broad St. (45)
1934. McCouch, Grayson P., Univ. of Pa. School of Medicine (4)
1938. McCrea, Lowrain E., 1930 Chestnut St. (3)
1958. McCune, Wallace G., 5555 Wissahickon Ave., (44)
1937. McCutcheon, Morton, Cambridge Apts. (44)
1942. McDonald, P. Robb, Lankenau Medical Bldg. (51)
1953. McDonnell, William V., West Jersey Hospital, Camden 4, N. J.
1952. McElroy, Robert C., 133 S. 36th St. (4)
1950. McFadden, William M., 1187 E. Washington Lane (38)
1949. McGavic, John S., 601 Montgomery Ave., Bryn Mawr, Pa.
1945. McGee, Lemuel Clyde, Hercules Powder Company, Wilmington, Del.
1954. McGehee, Edward H., 33 E. Chestnut Hill Ave. (18)
1952. McGlade, Thomas H., 719 Cooper St., Camden, N. J. M
1956. McGrath, Raymond J., 1720 Spruce St. (3)
1959. McKeown, John J., Jr., 1012 Walnut St. (7)
1933. McLaughlin, James S., 330 S. 9th St. (7)
1924. McMillan, Thomas M., 1901 Walnut St. (3)
1924. McPhedran, F. Maurice, Germantown Hosp., Penn and Chew Sts. (44)
1955. McStravog, Lawrence J., 6910 Market St., Upper Darby, Pa.
1954. MacFadyen, Bruce V., 135 S. 18th St. (3)
1943. MacFarlan, Douglas, 1805 Chestnut St. (3)
1932. Macfarlane, Catherine, 136 S. 16th St. (2)
1947. Machella, Thomas E., Univ. of Pa. Hospital (4)
1949. MacNeal, Perry Scott, 330 S. 9th St. (7)
1951. Mac Neish, W. J., 136 S. 16th St. (2)
1955. Macy, Dorothy, Jr., 705 Beechwood Road, Media, Pa.
1957. Madow, Leo, 111 N. 49th St. (39)
1935. Maeder, LeRoy M. A., 1910 Rittenhouse Sq. (3)
1952. Mahoney, J. Francis, 250 S. 18th St. (3)
1959. Mandel, Martin M., 255 S. 17th St. (3)
1942. Manges, Lewis C., Jr., 2001 Delancey Place (3)
1954. Manges, Willis E., Methodist Hospital, Broad & Wolf Sts. (48)
1959. Maniglia, Rosario, 230 N. Broad St. (2)
1949. Manlove, Francis R., 406 Surburban Sq., Ardmore, Pa.
1936. Mann, Bernard, 2019 Pine St. (3)
1960. Manning, Valentine R., 3336 Aldine St. (36)
1956. Manstein, George, 1351 Tabor Rd. (41)
1961. Mapow, Abraham B., 535 Pine St. (6)
1953. Marbach, A. Herbert, 1307 Tabor Rd. (41)
1948. Marden, Philip Ayer, 1910 Spruce St. (3)
1937. Margolies, Alexander, 2507 Chestnut St., Chester, Pa.
1958. Marino, Daniel J., 1422 Race St. (2)
1950. Mark, George E., 3401 N. Broad St. (40)

1950. Marshall, E. Wayne, Jr., 1520 Spruce St. (2)
1951. Martin, William L., Hahnemann Hospital. (2)
1952. Martucci, Albert A., 1460 E. Cheltenham Ave. (24)
1953. Marx, Halvey E., 76 Brennan Drive, Bryn Mawr, Pa.
1953. Massey, Franklin C., 122 Hillside road, Deepdale, Strafford, Pa.
1939. May, Hans, 255 S. 17th St. (3)
1951. Mayock, Robert L., 3600 Spruce St. (4)
1958. Mays, Ralph Whiteman, 154 W. Tulpehocken St. (44)
1961. Mechanick, Philip, Ford Rd. & Monument Ave. (31)
1952. Mecray, Paul, Jr., 405 Loucroft Ave., Haddonfield, N. J.
1951. Medinger, Frederick G., 1941 Woodland Road, Abington, Pa.
1959. Medoff, Joseph, 5400 Wynnefield Ave. (31)
1955. Melnick, Theodore, 1152 N. 63rd St. (31)
1941. Mendell, Theodore H., 2023 Spruce St. (3)
1951. Mendelssohn, Edwin, 1301 Tabor Rd. (41)
1943. Meranze, David R., 1031 Lakeside Ave. (26)
1954. Mertens-Roesler, Elizabeth, 224 W. School House Lane (44)
1956. Merves, Louis, 1015 Walnut St. (7)
1955. Mervine, Thomas B., 133 S. 36th St. (4)
1959. Metzger, Harry N., 1815 Pine St. (3)
1955. Meyer, Eugene A., 1438 Mt. Ephraim Ave., Camden, N. J.
1937. Meyer, George Phillip, 410 Haddon Ave., Camden, N. J.
1956. Miller, Bernard Joseph, 6013 Greene St. (44)
1935. Miller, Ford A., 4016 Chestnut St. (4)
1939. Miller, Malcolm W., Lankenau Medical Bldg. (51)
1939. Miller, Merle M., 6013 Greene St. (44)
1932. Miller, M. Valentine, 114 W. Phil-Ellena St. (19)
1921. Miller, T. Grier, 133 S. 36th St. (4)
1955. Miller, William H., Fitzgerald Mercy Hospital, Darby, Pa.
1952. Minehart, John R., 4821 Germantown Ave. (44)
1952. Mintz, S. S., 1930 Chestnut St. (3)
1937. Missett, Joseph Vincent, Jr., 2031 Locust St. (3)
1904. Mitchell, Charles Franklin, 2003 Pine St. (3)
1950. Mitchell, John McK., Univ. of Pa. School of Medicine (4)
1952. Mitchell, Robert McNair, 330 S. 9th St. (7)
1959. Mitterling, Robert C., Chestnut St. & Glendale Rd.; Upper Darby
1932. Mohler, Roy W., 1806 Spruce St. (3)
1936. Montgomery, Hugh, 119 Glenn Road, Ardmore, Pa.
1936. Montgomery, John B., 1930 Chestnut St. (3)
1932. Montgomery, Thaddeus L., 2031 Locust St. (3)
1935. Moore, John Royal, 3401 N. Broad St. (40)
1947. Moore, Matthew Thibaud, 1813 Delancey Pl. (3)
1958. Moore, Samuel R., Jr., 1600 Arch St. (1)
1958. Morani, Alma D., 3665 Midvale Ave. (29)
1936. Morgan, David R., Jefferson Medical College (7)
1944. Morris, Harold H., Villa Nova, Pa.
1945. Morris, I. Paul, 1939 Cheltenham Ave. (17)
1957. Moyer, David G., 701 W. Main St., Lansdale, Pa.
1959. Moyer, John H., 230 N. Broad St. (2)
1941. Mucklé, Craig Wright, 6 Craig Lane, Haverford, Pa.
1929. Mudd, Stuart, Department of Bacteriology, Univ. of Pa. School of Medicine (4)
1960. Mulberger, Robert D., 1930 Chestnut St. (3)

1949. Mulholland, Stanford W., 22nd & Parkway (3)
1934. Mullen, Edward A., 472 Roxborough Ave. (28)
1930. Murphy, Douglas P., 601 S. Bowman Ave., Merion Station, Pa.
1953. Murphy, Edward J., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1958. Murphy, John J., 3600 Spruce St. (4)
1959. Murray, Edwin N., 130 N. Broadway, Camden, N. J.
1955. Murtagh, Frederick, 3701 N. Broad St. (40)
1951. Myers, David, 3701 N. Broad St. (40)
1955. Nachod, Grace R., 5501 Greene St. (44)
1945. Naide, Meyer, 2034 Spruce St. (3)
1951. Naidoff, David, 3500 Tudor St. (36)
1950. Nardone, Anthony A., 912 S. 49th St. (43)
1959. Neal, Hunter, S., 406 Lankenau Medical Bldg. (51)
1958. Nealon, Thomas F., Jr., 1025 Walnut St. (7)
1948. Neese, Paul H., 17 Derwen Road, Cynwyd, Pa.
1936. Nelson, Guy M., 255 S. 17th St. (3)
1943. Nelson, Waldo E., 615 Moreno Rd., Narberth, Pa.
1955. Nemir, Paul, Jr., 419 S. 19th St. (46)
1935. Nicholson, Jesse Thompson, 1740 Bainbridge St. (46)
1960. Nicholson, John W., III, 115 Chestnut St., Moorestown, N. J.
1947. Noone, Ernest L., 4501 Cedar Lane, Drexel Hill, Pa.
1954. Norris, Charles M., 3401 N. Broad St. (40)
1905. Norris, George W., 250 S. 18th St. (3)
1938. Norris, Robert F., 513 Wynnewood Ave., Wynnewood, Pa.
1957. Oakey, Richard S., Jr., 309 Medical Bldg., Lankenau Hospital (51)
1947. O'Keefe, John J., 255 South 17th St. (3)
1954. Olsen, Axel K., 230 N. Broad St. (2)
1949. O'Neill, James F., 140 Roslyn Ave., Glenside, Pa.
1954. O'Neill, Thomas, J. E., Centinnial Bldg., Front St. & Lehigh Ave. (25)
1947. Ornsteen, A. M., 2007 Delancey Pl. (3)
1947. Ornston, Darius Gray, 415 Dresher Road, Horsham, Pa.
1936. Orr, Theodore E., 3815 Chestnut St. (4)
1958. O'Sullivan, Ward D., Misericordia Hospital (43)
1955. Ottenberg, Donald J., 3519 N. Broad St. (40)
1913. Outerbridge, George W., 1927 Spruce St. (3)
1961. Owen, Barbara J., Bryn Mawr Hospital, Bryn Mawr, Pa.
1949. Padis, Nicholas, Lankenau Medical Bldg. (51)
1954. Palmer, Louis H., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1909. Parish, Benjamin Dores, 704 Bethlehem Pike, Flourtown, Pa.
1945. Park, Felix Roman, 1980 Utica Sq., Tulsa, Okla.
1940. Parker, Alan P., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1948. Parkhurst, Leonard Woods, 330 S. 9th St. (7)
1952. Paxson, Newlin F., 245 N. Broad St. (7)
1932. Payne, Franklin L., Univ. of Pa. Hospital (4)
1954. Pearce, Alexander E., 1420 Race St. (2)
1958. Pearce, Rowan C., Jr., 514 Cooper St., Camden, N. J.
1943. Pearson, Gerald H. J., Presidential Apts.—Adams House (31)
1954. Pearson, Manuel M., 111 N. 49th St. (39)
1952. Peck, Roy I., 3400 Spruce St. (4)
1960. Peltz, William L., 111 N. 49th St. (39)
1930. Pendergrass, Eugene P., Univ. of Pa. Hospital (4)
1953. Penneys, Raymond, University of Pennsylvania Hospital (4)

1942. Perkins, William Harvey, The Lenox, 13th & Spruce Sts. (7)
1946. Perloff, William Harry, Albert Einstein Medical Center (41)
1953. Persky, Abram H., 1737 Chestnut St. (3)
1940. Pessel, Johannes F., 224 West State St., Trenton, N. J.
1952. Peters, Michael, 262 W. Broad St., Telford, Pa.
1961. Peterson, Lysle H., University of Pennsylvania (4)
1940. Pettit, Horace, Times Medical Bldg., Ardmore, Pa.
1949. Pettit, Mary DeWitt, 3343 W. Penn. St. (29)
1915. Pfeiffer, Damon B., Meadowbrook, Pa.
1946. Pfeiffer, Mildred C. J., 358 Valley Rd., Merion, Pa.
1935. Phillips, Arthur W., 3904 Walnut St. (4)
1961. Phillips, William A., Eastern Pennsylvania Psychiatric Institute (29)
1911. Piersol, George Morris, 308 Kent Rd., Wynnewood, Pa.
1948. Pierson, Daniel B., Jr., 740 Beacon Lane, Merion, Pa.
1961. Pike, Anne H., 5603 Greene St. (44)
1957. Pilling, George Platt, IV, 2600 N. Lawrence St. (33)
1933. Pillsbury, Donald M., Univ. of Pa. Hospital (4)
1957. Platt, Ruth M., 441 Lyceum Ave. (28)
1951. Poinsard, Paul J., 2031 Locust St. (3)
1937. Polk, David Stewart, Rosemont, Pa.
1956. Pontarelli, Domenic J., Rittenhouse Plaza, 1901 Walnut St. (3)
1953. Porreca, George, A., 1912 Spruce St. (3)
1932. Porter, Roland De Lance, Abington Medical Bldg., Abington, Pa.
1951. Post, Joseph W., 1930 Chestnut St. (3)
1951. Pote, Harry H., 103 E. Ridley Ave., Ridley Park, Pa.
1958. Potter, H. Phelps, Jr., Woman's Medical College (29)
1951. Pressman, Robert S., 170 W. Olney Ave. (20)
1947. Prickett, John A., Warrington, Bucks County, Pa.
1954. Prince, Leon N., 2025 Spruce St. (3)
1931. Pryor, Charles Allen, 255 S. 17th St. (3)
1952. Pugh, James E., 614 Church Lane, Yeadon, Pa.
1947. Putney, Floyd Johnson, 1712 Locust St. (3)
1958. Rachlin, Lillian, Veterans' Adm. Hosp., Sepulveda, Cal.
1943. Radbill, Samuel X, 7043 Elmwood Ave. (42)
1953. Radbill, Sidney G., 37 S. 20th St. (3)
1945. Rakoff, Abraham Edward, 269 S. 19th St. (3)
1953. Ralston, Edgar L., 3400 Spruce St. (4)
1931. Ramsey, Frank M., 620 E. Willow Grove Ave. (18)
1953. Ranieri, Tito A., 2320 S. Broad St. (45)
1941. Rankin, Charles A., Ludlow & Heather Rd., Upper Darby, Pa.
1946. Rapaport, Milton, Children's Hospital, 1740 Bainbridge St. (46)
1951. Rathmell, Thomas K., 446 Bellevue Ave., Trenton, N. J.
1926. Ravdin, I. S., Univ. of Pa. Hospital (4)
1956. Ravdin, Robert Glenn, 3400 Spruce St. (4)
1959. Raventos, Antolin, 3400 Spruce St. (4)
1961. Read, William T., Jr., Cooper Hospital, Camden, N. J.
1954. Reagan, Lindley B., 175 Madison Ave., Mt. Holly, N. J.
1960. Reed, Theodore P., Lankenau Medical Bldg. (51)
1928. Reese, Warren S., 2118 Locust St. (3)
1920. Rehfuss, Martin E., 131 St. George's Rd., Ardmore, Pa.
1921. Reiff, E. Paul, 1927 Spruce St. (3)
1919. Reimann, Stanley P., 703 W. Phil-Ellena St. (19)

1956. Reishtein, William A., 255 S. 17th St. (3)
1951. Rentschler, Laurence B., 5800 Ridge Ave. (28)
1945. Rhoads, Jonathan E., Univ. of Pa. Hospital (4)
1951. Richardson, Fred Mac D., 160 Carpenter Lane (19)
1919. Richardson, Russell, Phila. Tuberculosis Sanitorium #4, Corinthian & Girard Aves. (30)
1951. Riegel, Donald, 5110 Chester Ave. (43)
1942. Riggs, Helena E., 150 Hewitt Rd., Wyncote, Pa.
1936. Ritter, Joseph A., 2405 N. 54th St. (31)
1932. Robbins, Frederick R., 317 Milbank Rd., Bryn Mawr, Pa.
1952. Robbins, Robert, 3401 N. Broad St. (40)
1960. Robbins, William S., 255 S. 17th St. (3)
1954. Roberts, Brooke, 3400 Spruce St. (4)
1939. Roberts, Ella, 110 Cornell Ave., Swarthmore, Pa.
1957. Roberts, Joan Mary, 4 W. Mt. Pleasant Ave. (19)
1932. Robertson, Harold F., 2118 Pine St. (3)
1954. Robertson, Hugh, 255 S. 17th St. (3)
1938. Roche, Philip Q., Route 1, Conshohocken, Pa.
1961. Rodahl, Kaare, Lankenau Hospital Research (51)
1960. Roeder, Paul H., 330 S. 9th St. (7)
1955. Rogers, Fred B., 3401 N. Broad St. (40)
1951. Ronis, Bernard J., 2106 Spruce St. (3)
1948. Roscoe, Constantine R., 7226 Castor Ave. (24)
1928. Rose, Edward, 426 Owen Rd., Wynnewood, Pa.
1936. Rose, Elizabeth Kirk, 426 Owen Rd., Wynnewood, Pa.
1959. Rose, Isadore, 6000 W. Oxford St. (31)
1952. Rose, S. Brandt, Chestnut Hill Hospital (18)
1946. Rosemond, George Parrott, 3401 N. Broad St. (40)
1960. Rosenow, Edward C., Jr., American College of Physicians, 4200 Pine St. (4)
1948. Rothman, Maurice M., 1727 Spruce St. (3)
1951. Rouse, George P., Jr., 250 South 18 St. (2)
1952. Roxby, Bruce S., 5501 Greene St. (44)
1955. Roxby, John B., Jr., 4821 Germantown Ave. (44)
1949. Royster, Henry P., 3400 Spruce St. (4)
1941. Royster, Hubert A., Jr., 888 Glenbrook Ave., Bryn Mawr, Pa.
1959. Rubin, Alan, 255 S. 17th St. (3)
1952. Rubin, I. Edward, 255 S. 17th St. (3)
1933. Rudolphy, Jay Besson, 230 S. 21st St. (3)
1946. Rupp, Charles, 133 S. 36th St. (4)
1947. Rush, Alexander, 330 S. 9th St. (7)
1960. Russell, George W., 430 Greenwood Ave., Wyncote, Pa.
1945. Rynes, Samuel E., 334 S. 21st St. (3)
1952. Sain, Fletcher D., 8 Orchard Ave., Bristol, Pa.
1958. Sall, Manuel, 255 S. 17th St. (3)
1952. Salner, Nathan P., 6812 Castor Ave. (24)
1952. Saltzman, Maurice, 2037 Spruce St. (3)
1944. Sampson, David Alan, 726 Braeburn Lane, Penn Valley, Narberth, Pa.
1936. Sands, Joseph Evans, Tedyn Apts., Bryn Mawr, Pa.
1950. Sarner, Joseph B., 269 S. 19th St. (3)
1949. Saul, Leon J., Highland Ave., Media, Pa.
1908. Sautter, Albert C., Germantown Professional Bldg. (44)
1954. Savacool, J. Woodrow, 146 W. Tulpehocken St. (44)
1947. Sayen, John J., 3600 Spruce St. (4)

1948. Scarano, Joseph Albert, 1432 S. Broad St. (46)
1917. Schaeffer, J. Parsons, 4634 Spruce St. (39)
1929. Scheffey, Lewis C., 601 Walnut Lane, Haverford, Pa.
1942. Scheie, Harold G., 3400 Spruce St. (4)
1929. Schenck, Harry P., 1235 Wyngate Rd., Wynnewood, Pa.
1945. Schlezinger, Nathan S., 255 S. 17th St. (3)
1961. Schlosser, Woodrow D., 3701 N. Broad St. (40)
1917. Schnabel, Truman G., 1704 Pine St. (3)
1958. Schnabel, Truman G., Jr., Phila. General Hospital (4)
1957. Schnall, Nathan, 2037 Pine St. (3)
1928. Schofield, Frederick S., 1509 E. Barringer St. (50)
1955. Schreader, Charles J., 318 W. Godfrey Ave. (20)
1958. Schreck, Kenneth M., Temple Univ. School of Medicine (40)
1952. Schulz, Norbert J., 1901 Walnut St. (3)
1950. Schumann, Francis, 8811 Germantown Ave. (18)
1948. Schwarz, Gabriel A., 133 S. 36th St. (4)
1955. Schwegman, Cletus W., Hospital of the University of Penna. (4)
1930. Scott, John Porter, Children's Hospital, 1740 Bainbridge St. (46)
1950. Scott, Michael, 3401 N. Broad St. (40)
1940. Scott, T. F. McNair, Children's Hospital, 1740 Bainbridge St. (46)
1952. Seifer, Arthur F., 3401 N. Broad St. (40)
1954. Seifter, Joseph, Wyeth Institute for Medical Research (1)
1957. Seipel, Russell C., 6000 Jefferson St. (31)
1958. Sellers, Alfred M., Hosp. of the Univ. of Pa. (4)
1952. Semisch, Charles W., III, 5329 Rising Sun Ave. (20)
1961. Sencindiver, Paige V., 2228 S. Broad St. (45)
1958. Shafer, Albert H., 1004 E. Cherry Hill Apts., Merchantsville 10, N. J.
1960. Shannon, Gerard M., 1434 E. Hunting Park Ave. (24)
1950. Sharp, Reuben L., 719 Cooper St., Camden, N. J.
1928. Sharpless, Frederick C., 621 Railroad Ave., Haverford, Pa.
1956. Shaw, Daniel L., Jr., 702 Knox Rd., Villanova, Pa.
1948. Shay, Harry, 3400 N. Broad St. (40)
1955. Shechter, Fred R., 2461 No. 54th St. (31)
1954. Shelley, Walter B., 36th & Spruce Sts. (4)
1955. Shenkin, Henry A., Episcopal Hospital (25)
1946. Shepherd, Samuel Garfield, 2039 Pine St. (3)
1932. Sheridan, Joyce T., 412 W. Durham St. (19)
1956. Sherson, Jacob S., 131 Channing Ave., Malvern, Pa.
1936. Shipman, James Shelby, 255 S. 17th St. (3)
1958. Shipps, Hammell P., 719 Cooper St., Camden 2, N. J.
1957. Shope, Edward Pierce Lentz, 807 Wilson Bldg., Camden, N. J.
1946. Shoup, George Daniel, 121 W. Walnut Lane (44)
1955. Shubin, Harry, 6601 N. 21st St. (38)
1952. Shuman, Charles R., 3401 N. Broad St. (40)
1949. Sidlick, David M., 255 S. 17th St. (3)
1941. Silcox, Louis E., Lankenau Medical Bldg. (51)
1956. Sillars, Charles H., Abington Memorial Hospital, Abington, Pa.
1955. Silverstein, Alexander, 2114 Pine St. (3)
1961. Simmons, Vaughan P., The Fidelity Mutual Life Insurance Co. (1)
1954. Singmaster, Lawrence, Lankenau Medical Bldg. (51)
1952. Skromak, Stanley J., 5108 Torresdale Ave. (35)
1958. Sloviter, Henry A., 3400 Spruce St. (4)

1929. Smith, Austin T., 330 S. 9th St. (7)
1955. Smith, J. Winslow, 3034 Darby Rd., Ardmore, Pa.
1933. Smith, Lauren Howe, 111 N. 49th St. (39)
1952. Smith, Richard T., 330 S. 9th St. (7)
1927. Smyth, Calvin Mason, Abington Memorial Hospital, Abington, Pa.
1951. Snape, William J., 573 Stevens St., Camden, N. J.
1938. Snodgrass, L. E., 709 Walnut St. (6)
1953. Snyder, G. Gordon, Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1958. Sodeman, William A., 1025 Walnut St. (7)
1961. Soffe, Alvin M., 1930 Chestnut St. (3)
1935. Sokoloff, Martin J., 255 S. 17th St. (3)
1951. Solis-Cohen, Leon, 1530 Locust St. (2)
1940. Soloff, Louis A., 3401 N. Broad St. (40)
1950. Somerville, William J., 37 S. 20th St. (3)
1944. Sommer, George N. J., Jr., 120 W. State St., Trenton, N. J.
1952. Sones, Maurice, Mt. Airy Medical Bldg. (19)
1951. Sonneborn, Duane G., 1200 W. Erie Ave. (24)
1928. Spaeth, Edmund B., 1930 Chestnut St. (3)
1958. Spaeth, Philip G., 1930 Chestnut St. (3)
1937. Spangler, John Luther, Devon, Pa.
1957. Spelman, Joseph Worcester, Dept. of Public Health, 13th & Wood Sts. (7)
1935. Spiegel, Ernest A., 6807 Lawnton Ave. (26)
1961. Spiegelman, Jay, Benson East Apt., Jenkintown, Pa.
1955. Spitz, Eugene B., Children's Hospital (46)
1958. Splendido, Joseph A., 608 W. Clivedon (19)
1961. Stahlgren, LeRoy H., 133 S. 36th St. (4)
1960. Stainback, William C., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1957. Stanley, Robert C. G., 2315 Edgemont Rd., Chester, Pa.
1927. Starr, Isaac, 505 Cresheim Valley Rd. (18)
1952. Stauffer, Herbert M., 3401 N. Broad St. (40)
1952. Stayman, Joseph W., Jr., Germantown Hospital (44)
1945. Stecher, H. Armin, 1510 Darby Rd., Havertown, Pa.
1955. Steel, Howard H., 3401 N. Broad St. (40)
1952. Steiger, William A., 3401 N. Broad St. (40)
1946. Stein, Irvin, 1936 Spruce St. (3)
1953. Stein, Raymond O., 269 S. 19th St. (3)
1936. Steinfield, Edward, 2200 Benjamin Franklin Parkway (30)
1951. Sterling, Julian A., 1008 Sharpless Rd. (26)
1948. Stevens, Lloyd W., 133 S. 36th St. (4)
1928. Stokes, Joseph, Jr., Children's Hospital, 1740 Bainbridge St. (46)
1943. Stokes, S. Emlen, 129 Chester Ave., Moorestown, N. J.
1954. Stone, Hrant H., E. Shawmont Ave. (28)
1952. Stoner, Emery K., 222 E. Mt. Pleasant Ave. (19)
1961. Strang, John E., 330 S. 9th St. (7)
1953. Strawbridge, Rendall R., Lankenau Medical Bldg. (51)
1937. Strumia, Max M., Penn Valley, Narberth, Pa.
1960. Strumia, Paul V., Bryn Mawr Hospital, Bryn Mawr, Pa.
1937. Sturgis, Margaret C., 349 Wistar Rd., Wynnewood, Pa.
1927. Sturgis, Samuel Booth, 349 Wistar Rd., Wynnewood, Pa.
1961. Sullivan, Andrew A., 5455 Trinity Place (43)
1961. Sullivan, Benjamin H., Jr., 1830 Rittenhouse Square (3)
1934. Summey, Thomas J., Burlington County Hosp., Mt. Holly, N. J.

1930. Sunderman, F. William, 1833 Delancey Place (3)
1961. Sunderman, F. William, Jr., 1025 Walnut St. (7)
1954. Sussman, Marcel S., 101 S. 20th St. (3)
1952. Sweeney, Francis X., 2412 E. Allegheny Ave. (34)
1955. Taggart, Harold A., 235 N. 15th St. (2)
1952. Talbot, Timothy R., Jr., 204 Booth Lane, Haverford, Pa.
1943. Tassman, Isaac S., 136 S. 16th St. (2)
1946. Tauber, Robert, 2019 Walnut St. (3)
1952. Taylor, Ann Gray, 6364 Germantown Ave. (44)
1960. Taylor, Daniel B., 2241 Federal St. (46)
1956. Templeton, John Y., III, 1025 Walnut St. (7)
1951. Theodos, Peter A., 1930 Chestnut St. (3)
1961. Therman, Per-Olof, 111 N. 49th St. (39)
1959. Thomas, Arthur H., 5240 Vine St. (39)
1946. Thomas, Carmen C., 1930 Chestnut St. (3)
1952. Thompson, Charles M., 255 S. 17th St. (3)
1961. Thompson, James C., 803 Spruce St. (7)
1927. Thorington, J. Monroe, 37 S. 20th St. (3)
1936. Thorp, Francis Quicksall, 4900 Penn St. (24)
1936. Thudium, William J., 700 Merion Square Rd., Gladwyne, Pa.
1954. Tindall, Dorothy D., 37 S. 20th St. (3)
1935. Tocantins, Leandro Maués, 1025 Walnut St. (7)
1935. Toland, Owen J., Episcopal Hospital, Front and Lehigh Aves. (25)
1952. Tondreau, Roderick L., 6470 Drexel Rd. (31)
1959. Toole, James F., Univ. of Pa. Hospital, 3400 Spruce St. (4)
1949. Torany, Anthony S., 2038 Locust St. (3)
1945. Tourish, William J., 1124 Woodmont Rd., Gladwyne, Pa.
1936. Towson, Charles Emory, 224 W. Washington Lane (44)
1955. Trimpi, Howard D., 501 N. 17th St. Allentown, Pa.
1954. Trommer, Philip R., 258 S. 18th St. (3)
1956. Troncelliti, Mario V., Pennsylvania Hospital (7)
1953. Tropea, Frank, Jr., 500 Mulberry Lane, Haverford, Pa.
1947. Trueman, Robert H., 2101 Chestnut St. (3)
1954. Truitt, R. Marshall, Jr., 740 Westview St. (19)
1959. Tuddenham, William J., 3400 Spruce St. (4)
1938. Tuft, Louis, 1530 Locust St. (2)
1933. Tumen, Henry J., 1830 Rittenhouse Square (3)
1938. Turman, Christopher M., Wyncote, Pa.
1923. Turner, Creighton, H., 1731 Pine St. (3)
1954. Turner, Linton W., 3401 N. Broad St. (40)
1929. Tyson, Ralph M., 6709 N. 8th St. (26)
1959. Tyson, R. Robert, 3401 N. Broad St. (40)
1937. Uhle, Charles A. W., Lankenau Medical Bldg. (51)
1953. Ulin, Alexander, W., 230 N. Broad St. (2)
1907. Ullom, Josephus T., Carpenter and Quincy Sts. (19)
1960. Uricchio, Joseph F., 1422 Race St. (2)
1950. Valdes-Dapena, Antonio, 3006 Midvale Ave., Phila. (29)
1958. Van den Noort, Gordon S., 888 Glenbrook Ave., Bryn Mawr, Pa.
1937. Vander Veer, Joseph B., 330 S. 9th St. (7)
1937. Van Loon, Emily Lois, 1930 Chestnut St. (3)
1960. Van Meter, Ralph H., 244 W. Main St., Moorsetown, N. J.
1933. Vastine, Jacob H., 2nd, 136 S. 16th St. (2)

1958. Velkoff, Cyril L., 2100 Walnut St. (3)
1955. Viek, Peter, 1941 Woodland Rd., Abington, Pa.
1952. Vischer, Thomas J., 5903 Greene St. (44)
1940. Voegelin, Adrian W., Germantown Professional Bldg. (44)
1941. Vogel, Stoughton R., 151 W. Tulpehocken St. (44)
1960. Wagenheim, Harry H., 1822 Spruce St. (3)
1949. Wagner, Frederick B., Jr., 800 Chauncy Road, Narberth, Pa.
1949. Wagner, Joseph A., 201 Highland Ave., Bryn Mawr, Pa.
1954. Wainer, Amos S., 1621 Spruce St. (2)
1938. Waldman, Joseph, 404 Meadowbrook Lane (18)
1955. Waldron, Jerome M., 2300 Cheltenham Ave. (50)
1932. Walkling, Adolph A., 136 S. 16th St. (2)
1955. Warner, Halsey F., 100 W. Coulter St. (44)
1956. Watkins, E. Lloyd, 8815 Germantown Ave. (18)
1954. Waugh, Elizabeth S., 348 Greene Lane (28)
1952. Weaver, Harry S., Jr., 37 S. 20th St. (3)
1955. Weaver, Robert L., 26 Henley Rd. (31)
1953. Weber, Lennard L., 255 S. 17th St. (3)
1957. Webster, Marie Blanchefield, 3044 N. 5th St. (33)
1930. Weeder, S. Dana, 250 W. Tulpehocken St. (44)
1954. Weiner, Louis H., Carlene Apts. 2500 Belmont Ave. (31)
1952. Weinstein, George L., 255 S. 17th St. (3)
1950. Weiss, Sidney, 1930 Chestnut St. (3)
1959. Wellenbach, Burton L., 255 S. 17th St. (3)
1951. Welty, Jack W., Montgomery Ave. & Owen Rd., Wynnewood, Pa.
1955. Wendkos, Martin H., Latches Lane Apts., Merion, Pa.
1961. Wermuth, William C., 111 N. 49th St. (39)
1959. West, Clifton F., Jr., 406 Lankenau Medical Bldg. (51)
1959. Whayne, Tom F., 36th & Spruce Sts. (4)
1935. Whelan, G. L., 2100 Walnut St. (3)
1921. Whitaker, William, 4645 Oakland St. (24)
1936. White, Ellen Pawling Corson-, Gladwyne, Pa.
1960. Whiteley, William H., 1015 Chestnut St. (7)
1925. Widmann, Bernard P., 250 S. 18th St. (3)
1954. Wieder, Henry S., Jr., 330 S. 9th St. (7)
1939. Willauer, George, 6129 Greene St. (44)
1937. Williams, John C., 6370 Germantown Ave. (44)
1920. Williams, Philip F., 256 Broughton Lane, Villanova, Pa.
1950. Williams, R. G., Univ. of Pa. School of Medicine (4)
1927. Williamson, Ernest G., 6353 Woodbine Ave. (31)
1949. Willson, J. Robert, 3401 N. Broad St. (40)
1945. Wilson, John F., 2013 Delancey Pl. (3)
1937. Wilson, Ross B., Lankenau Medical Bldg. (51)
1949. Wilson, William W., 133 S. 36th St. (4)
1957. Winkelman, N. William, Jr., 4141 Apalogen Rd. (44)
1948. Winston, Julius, 5839 Chester Ave. (43)
1941. Wirts, C. Wilmer, 2017 Delancey St. (3)
1961. Wise, Robert I., 1025 Walnut St. (7)
1953. Wohl, George T., Philadelphia General Hospital (4)
1933. Wohl, Michael G., 1727 Pine St. (3)
1958. Woldow, Irving, Einstein Med. Center, York & Tabor Rds. (41)
1958. Wolf, John H., 124 W. Walnut Lane (44)

1944. Wolf, Lewis R., 3474 Frankford Ave. (34)
1918. Wolferth, Charles C., 133 S. 36th St. (4)
1962. Wolferth, Charles C., Jr., 230 N. Broad St. (2)
1957. Wolgamot, John R., 244 W. Main St., Moorestown, N. J.
1957. Wolkowicz, Michael I., 2022 Spruce St. (3)
1942. Wolman, Irving J., 7607 Woodlawn Ave. (26)
1932. Wood, Francis C., 212 Laurel Lane, Haverford, Pa.
1944. Wood, H. Curtis, Jr., Skippack Pk., Whitemarsh, Pa.
1953. Woodruff, Marston T., 4940 Penn St. (24)
1928. Wright, Carroll S., 1402 Spruce St. (2)
1960. Wurzel, Harold A., 3400 Spruce St. (4)
1960. Yanoff, Jacob, 1000 Johnston St. (48)
1921. Ylvisaker, Lauritz S., 429 Montgomery Ave., Haverford, Pa.
1941. Young, Barton R., Germantown Hospital (44).
1961. Zanni, Anthony L., 111 N. 49th St. (39)
1957. Zaslow, Jerry, 1351 Tabor Rd. (41)
1955. Zatuchni, Jacob, 3401 N. Broad St. (40)
1946. Zeigerman, Joseph H., 2105 Spruce St. (3)
1949. Zintl, William J., 69th & Market Sts., Upper Draby, Pa.
1956. Ziserman, Abraham J., 2046 Pine St. (3)
1933. Zulick, J. Donald, Abington Memorial Hospital, Abington, Pa.

Non-Resident Fellows

ELECTED

1912. Addison, William H. F., 266 East Sidney Avenue, Mt. Vernon, N. Y.
1947. Allbritten, Frank F., Jr., Univ. of Kansas Medical Center, Kansas City 3, Kansas.
1960. Ames, Mary Daniel, 2039 N. 2nd St., Harrisburg, Pa.
1941. *Aronson, Ronald S., 9401 Byeforde Road, Kensington, Md.
1954. Austin, George M., University of Oregon Medical School, Portland, Oregon.
1942. Bachman, Carl, Rutherford, Napa Co., Calif.
1931. Bates, William, Harrisburg Hospital, Harrisburg, Pa.
1932. Behney, Charles A., Dept. of Health, Old DeWitt Rd., Lansing, Mich.
1955. Blank, Harvey, Jackson Memorial Hospital, Miami 36, Fla.
1921. Borzell, Francis F., R. D. 2, Box 2051, Browns Mills, N. J.
1937. Braceland, Francis J., The Institute of Living, 200 Retreat Ave., Hartford, Conn.
1951. Brinton, S. Jervis, 245 Coral Lane, Palm Beach, Fla.
1948. *Brown, Robert B., U. S. Naval Hospital, Bethesda, Md.
1953. Burbidge, J. Raymond, 163 Nassau St., Princeton, N. J.
1957. Butterworth, Thomas, 411 Walnut St., Reading, Pa.
1948. Chapman, John P., Calle Fray Junipero Serra 26, Palma de Mallorca, Balearic Islands, Spain.
1950. Chapple, Charles C., 1500 Massachusetts Ave., N.W., Washington, D. C.
1941. Cheleden, John, 1012 Volusia Ave., Daytona Beach, Fla.
1930. Clarke, Francis Mann, 116 New St., New Brunswick, N. J.
1926. Clerf, Louis H., 5575–8th Ave., North St. Petersburg, Fla.
1930. Cottrell, James E., 623 Latona Ave., Trenton 8, N. J.
1959. *Cowan, Capt. John S., U. S. Atlantic Fleet, P.O. Box 100, Norfolk 11, Va.
1960. Cowley, Allen W., Sr., 1919 N. Front St., Harrisburg, Pa.
1940. Crowe, Aldrich C., 1208 Ocean Ave., Ocean City, N. J.

* Military service.

1947. Cutler, Norman L., 1300 Harrison St., Wilmington, Del.
1941. *Cuttle, Tracy D., Marine Corps Recruit Depot, San Diego (40) Calif.
1955. Daugherty, J. Arthur, 1511 N. Front St., Harrisburg, Pa.
1954. Deitrick, John E., Cornell Medical College, 1300 York Ave., New York 21, N. Y.
1941. Dixon, Harold M., 4805 46th St., N.W., Washington 16, D. C.
1953. Dixon, James P., Antioch College, Yellow Springs, Ohio.
1961. Duane, Thomas D., 619 Main St., Bethlehem, Pa.
1937. Dunn, Charles W., Grange Ave., Collegeville, R.D. #1, Pa.
1959. Durgin, Bernice Elise, 221 N. Allegheny St., Bellefonte, Pa.
1955. Edwards, Margaret Hay, 1100 Edgewood Ave., Trenton, N. J.
1953. Eisenberg, Isadore J., 1520 N. 2nd St. Harrisburg, Pa.
1951. Ellis, Mackinnon, 121 Mill Rock Rd., Hamden, Conn.
1957. *Errion, Arthur Robbins, U. S. Naval Hospital, Bethesda, Md.
1951. Ervin, Carl E., 240 North Third Street, Harrisburg, Pa.
1944. Estes, W. L., Jr., 35 E. Elizabeth Ave., Bethlehem, Pa.
1954. Evans, Harry D., Jr., American Cyanamid Co., 1 Caspar St., Danbury, Conn.
1952. Faller, Constantine P., 127 State St., Harrisburg, Pa.
1940. Forrester, James S., Harrisburg Polyclinic Hospital, Harrisburg, Pa.
1951. Friedland, Carl K., 271 W. Blackwell St., Dover, N. J.
1947. Gaskill, Herbert S., 250 Ash St., Denver, Colo.
1913. Gates, Nathaniel, 10 Peterboro Ave., Detroit, Mich.
1958. Geckeler, George D., Tranquility, S. Windham, Vt.
1957. Giering, John Fleming, 84 James St., Kingston, Pa.
1931. Gilman, Robert Louis, Cheyney, Pa.
1954. Godfrey, Ellwood W., Princeton Hospital, Princeton, N. J.
1928. Gordon, Burgess L., The Lovelace Foundation, Albuquerque, New Mexico.
1952. Grieco, Reynold M., 2 W. 4th St., Williamsport, Pa.
1952. Gross, Elmer R., Medical Arts Bldg., Wilmington, Del.
1933. Gruber, Charles M., 1313 College Ave., Redlands, Calif.
1935. Haines, Harlan F., 231 N. Pine St., Seaford, Del.
1939. Hamblock, Leonard C., R.D. 2, Mt. Joy, Pa.
1955. Harris, John H., 1301-A N. Second St., Harrisburg, Pa.
1936. Hatch, Lerleen Clement, 2184 Ayres Ave., Akron, Ohio.
1947. Hawthorne, Herbert R., 1016 Yardley Rd., Morrisville, Pa.
1928. Hayman, Joseph Marchant, Jr., Tufts College Medical School, Boston, Mass.
1946. Hendrickson, Frank O., Jupiter, Fla.
1944. Hershey, J. Ivan, VA Hospital, Shreveport, La.
1955. Hills, Arthur G., 1000 N. W. 17th St., Miami, Fla. (36)
1933. Hitzrot, Lewis H., Medical Director, Mercersburg Academy, Mercersburg, Pa.
1950. Horn, Robert C., Henry Ford Hospital, Detroit, Mich.
1953. Imber, Irving, 428 Walnut St., Reading, Pa.
1958. Impink, Robert R., 405 Oley St., Reading, Pa.
1935. Ingleby, Helen, The Church House, Heacham, King's Lynn, England.
1921. Ivy, Robert H., 104 Dalton Rd., Paoli, Pa.
1952. Jones, Ralph, Jr., Jackson Memorial Hospital, Miami, Fla.
1955. Jordan, Charlotte B., 519 Sarah St., Stroudsburg, Pa.
1955. Jordan, Claus G., 519 Sarah St., Stroudsburg, Pa.
1956. Keffer, William H., 413 Oley St., Reading, Pa.
1947. Kelchner, Clyde H., 1125 Turner St., Allentown, Pa.
1944. LaMotte, William O., Brook Hill Farms, Hockessin, Del.
1954. LaMotte, William O., Jr., Professional Bldg., Wilmington 3, Del.
1952. Levan, John B., 401 Oley St., Reading, Pa.

1949. Lhamon, William T., Baylor University College of Medicine, Houston, Tex.
1954. Light, John J. B., 25 N. 9th St., Lebanon, Pa.
1954. Lindenmuth, Woodrow W., VA Hospital, West Haven, Conn.
1948. Livingood, Clarence S., Henry Ford Hospital, Detroit 2, Mich.
1933. Long, Esmond R., Conifer, Pedlar Mills, Va.
1919. Lynch, Frank B., Jr., U. S. Veterans Hospital, Coatesville, Pa.
1948. McCall, Milton L., Elizabeth Steel Magee Hospital, Pittsburgh Pa. (13)
1948. McLaughlin, John T., 1252 S. Central Ave., Glendale, Calif.
1950. Mackmull, Gulden, Camarillo State Hospital, Camarillo, Calif.
1953. Margolies, Michael, 567 E. Chestnut St., Coatesville, Pa.
1955. Margolies, M. Price, 567 E. Chestnut St. Coatesville, Pa.
1935. Mason, James B., 40 E. Erie St., Chicago 11, Ill.
1932. Meade, Richard H., Jr., 750 San Jose Dr., Grand Rapids, Mich.
1936. Middleton, William Shainline, Veteran's Administration, Washington, D. C.
1946. Miller, Franklin R., Snyder-Jones Clinic, First Nat. Bk. Bldg., Winfield, Kansas.
1928. Moon, Virgil H., Univ. of Miami, Coral Gables, Fla.
1949. Motley, Hurley L., 1212 Shatto St., Los Angeles, Calif.
1950. Neefe, John R., 627 Eleventh St., St. Petersburg, Fla.
1937. Nicholson, Samuel T., 2d, 642 High St., Pottstown, Pa.
1960. Ojers, Gaylord W., 619 Main St., Bethlehem, Pa.
1956. Oppenheimer, Albert, 224 E. Main St., Moorestown, N. J.
1926. Paul, John Rodman, Dept. Preventive Medicine, Yale University, New Haven, Conn.
1959. Pendergrass, Henry P., Massachusetts General Hospital, Boston, Mass.
1950. Pincus, Irwin J., Cedars of Lebanon Hospital, Los Angeles, Calif.
1922. Pleasants, Henry, West Chester, Pa.
1953. Raffensperger, Edward C., 2039 N. 2nd St., Harrisburg, Pa.
1938. Read, Hilton S., 5407 Atlantic Ave., Atlantic City, N. J.
1958. Reinhardt, David J., III, 1303 Delaware Ave., Wilmington, Del.
1936. Reisinger, John A., 901 20th St., N.W., Washington, D. C.
1955. Rettew, Philip L., 612 Museum Rd., Reading, Pa.
1961. Richardson, Herschel E., 2500 W. Central Ave., Toledo, Ohio
1947. Rogers, Arthur Merriam, 1351 Durwood Drive, Charlotte, N. C.
1907. Royer, B. Franklin, 429 E. Baltimore St., Greencastle, Pa.
1956. Rubenstone, Albert I., Michael Reese Hosp., Chicago, Ill.
1954. Sampson, Martin C., Schering Corp., Bloomfield, N. J.
1945. Schell, James F., 506 Sharpley Lane, Wilmington, Del.
1921. Schumann, Edward A., 4141 Jackson Drive, Lafayette Hill, Pa.
1951. Seitchik, Joseph, Sinai Hospital of Baltimore, Baltimore, Md.
1941. Shands, Alfred R., Jr., Alfred I. duPont Institute, Rockland Rd., Wilmington, Del.
1908. Shannon, Charles E. G., 9 Park St., Waterville, Maine.
1950. Shiffer, Paul H., Dreher Ave., R.D. #2, Stroudsburg, Pa.
1951. Shorey, Winston K., 46 Wingate Drive, Little Rock, Ark.
1933. Smelzer, Donald C., Lancaster General Hospital, Lancaster, Pa.
1954. Smith, Charles W., 128 State St., Harrisburg, Pa.
1929. Sponsler, Marshall B., 103 Lansdowne Road, DeWitt, N. Y.
1953. Steele, Brandt F., 717 Pontiac St., Denver 20, Colo.
1952. Steele, Eleanor, 717 Pontiac St., Denver 20, Colo.
1942. Stengel, Alfred, Jr., 75 Highland St., Holden, Mass.
1955. Stevenson, Theodore D., Presbyterian Board of Foreign Missions, 156 Fifth Ave., New York 10, N. Y.
1934. Stewart, Sloan G., Pacific and North Carolina Avenues, Atlantic City, N. J.
1931. Stiles, Merritt H., E. 406 14th Ave., Spokane 3, Wash.

1953. Stroud, Morris W., 3rd, Harvard Rd., Cleveland, Ohio.
1944. Swenson, Paul C., Veterans Hosp. Columbia, S. C.
1931. Taylor, Norman H., Queen of the East, E. Broadway, Hamilton, Bermuda.
1928. Thomas, J. Earl, Loma Linda University, Loma Linda, Calif.
1942. Thompson, Wesley D., 247 E. 3rd St., Lewistown, Pa.
1941. Tompkins, Pendleton, 450 Sutter St., San Francisco, Calif.
1897. Veasey, Clarence A., 1118 W. 9th Ave., Spokane 9, Wash.
1933. Waygood, James L., Pocono Pines, Pa.
1941. Weaver, Ruth H., 108 Atlantic Ave., Atlantic City, N. J.
1936. Wilder, Theodore S., Beckley Memorial Hospital, Beckley, W. Va.
1935. Willard, John H., Harlan Memorial Hospital, Harlan, Kentucky.
1953. Wilson, Julius L., Natl. Tuberculosis Assn., 1790 Broadway, New York City (19)
1953. Zarafonetis, Chris J. D., Simpson Memorial Institute, University of Michigan, Ann Arbor, Mich.

Honorary Fellows

Limited to Fifty, of Whom Twenty May be Foreigners.

American

ELECTED

1959. Fay, Marion, B.A., M.A., PH.D., SC.D.(HON.), LL.D.(HON.), Woman's Medical College, Henry Ave. & Abbottsford Rd. (29)
1936. Richards, Alfred Newton, PH.D., SC.D.(HON.), M.D.(HON.), LL.D.(HON), Emeritus Professor of Pharmacology, School of Medicine, and Associate Trustee, University of Pennsylvania. (4)
1958. Shryock, Richard H., PH.D., American Philosophical Society, Independence Square (6)
1947. Stone, Robert Spencer, M.D., University of California Medical School, San Francisco, Cal.

Foreign

1937. Dale, Sir Henry Hallet, C.B.E., F.R.S., M.A., M.D., F.R.C.P., 52 Queen Anne St., London, W. 1, England.
1955. Mann, Ida, M.A., D.SC., M.B., B.S., L.R.C.P., D.O.M.S., F.R.C.S., Ophthalmic Consultant to the Government of W. Australia, 56 Hobbs St., Nedlands, Perth, W. Australia.
1962. Schweitzer, Albert, PH.D., TH.D. M.D., D.D.(HON.), MUS.D.(HON.), LL.D.(HON.), O.M., Lambaréné Hospital, Lambaréné, Gabon Republic, W. Africa.

Honorary Associate Fellows

1955. Clement, Martin W., 6 Penn Center Plaza (4)
1955. Diemand, John A., President, Insurance Company of North America, 1600 Arch St. (2)

Necrological List

Resident Fellows	*Date of Election*	*Date of Death*
Bach, Theodore F.	May 6, 1935	January 18, 1962
Cohen, Frank L.	March 6, 1957	September 10, 1961
DeLong, Perce	October 3, 1923	March 12, 1961
Eads, John T.	January 7, 1935	February 6, 1962
Giordano, Anthony A. S.	January 12, 1931	April 17, 1961
Griffiths, John E.	October 3, 1945	July 8, 1961
Janton, O. Henry	March 7, 1952	February 14, 1962

Knipe, Norman L.	November 5, 1919	July 23, 1961
Lewis, James P.	January 10, 1938	October 24, 1961
Matthews, Robert A.	May 6, 1935	June 23, 1961
Norris, Charles C.	April 5, 1905	February 26, 1961
O'Neal, Alexander H.	June 4, 1913	June 25, 1961
Pepper, O. H. Perry	January 7, 1914	January 28, 1962
Percival, Milton F.	October 4, 1916	January 17, 1962
Shuster, Benjamin H.	January 6, 1936	October 1, 1961
Stokes, John H.	May 11, 1925	February 23, 1961
Wood, Dorothy D.	October 4, 1950	July 1, 1961

Non-Resident Fellows	*Date of Election*	*Date of Death*
Bank, Joseph	January 8, 1934	May 16, 1961
de Schweinitz, George L.	October 1, 1913	May 13, 1961
Eberhard, Theodore P.	February 4, 1953	August 14, 1960
Howell, John C.	March 2, 1938	June 10, 1961
Siegel, Alvin E.	May 9, 1932	December 10, 1961
Stockwell, Eunice LeBaron	January 4, 1949	November 19, 1961
Wood, Horatio C., III	January 8, 1952	September 5, 1961

(*Suggested Form of Bequest*)

I hereby give, devise, and bequeath to the College of Physicians of Philadelphia, a charitable and educational association organized under the laws of the Commonwealth of Pennsylvania and the executive offices whereof are located in the City of Philadelphia, the sum of.....

a. which sum shall be used for the general purposes of said association;

b. which sum shall be added to and become a part of the general endowment fund of said association;

c. which sum shall be used by said association preferably for the following purposes:

Index to Volume 29

1961–1962

Acupuncture, history, 212
Africa, health problems, 17, medical education, 17
Allen, G. S., 226*
Alvarenga prize lectures: Merrill, J. P., 1; Kety, S. S., 101
Anders lectures, McKusick, V. A., 112; Rutstein, D. D., 170
Anemia, apastic, chloramphenicol-induced, 214
Antazoline, antiarrhythmic properties, 217
Anticoagulant therapy, hemorrhagic complications, 218
Appel, K. E., 187
Atkinson, J. B., 224*
Auerbach, V. H., 90, 215

Bachman, C., 158
Bacon, H. E., 225*
Baird, H. W., III, 211
Baker, H. W., 224*
Baldridge, R. C., 215
Barker, E. S., 81
Békésy, otologic test, 213
Bequest, suggested form, 251
Berkowitz, D., 212, 216
Biochemistry, contributions to psychiatry, 101
Blake, J. B., 153
Blakemore, W. S., 224*
Bloom, S. M., 213
Blumberg, J. M., 223
Blumstein, G. I., 225*
Boucot, K. R., 223, 224*
Bower, J. O., memoir of, 48
Brauer, R. W., Newbold lecture, 49
Brest, A. N., 83, 88
Brigham, M. P., 215
Brobeck, J. R., 224*
Brody, H., 224*
Brooks, F. P., 211, 225*
Burnett, W. E., 225*
Burney, L. E., Hitchens lecture, 164

Camp, W. P., 127
Cannon, E. J., 212
Cantarow, A., 95, 224*
Caswell, H. T., 212
Cerebral ventricles, early history, 211
Channick, B. J., 220
Chessen, J., 212
Chevrett, L., 212
Chirico, A. M., 225*, 226*

* Refers to the list of College officers, committees, sections, and administrative staff.

Chloramphenicol, aplastic anemia, 214
Chlorothiazide, effect on serum lipids, 217
Chordae tendinae, ruptured, 218
Chun, R. B. D., 90
Cineradiography, clinical and experimental, 84; gastrointestinal, 86; cardiovascular, 89
Civil war, University of Pennsylvania Medical Alumni, 212; surgical wound infections, 212
Clark, J. E., 82, 221
Clark, T. W., 213
Clarke, E., 211
Coates, G. M., first memorial lecture, 213
Collections, College: annual report, 209
College of Physicians of Phila.: Adm. staff, 226; Collections (ann. rep.), 209; Committees, 224; Fellows, 227; Lectures (1960), 223; Library (ann. rep.), 200; Mütter Museum (ann. rep.), 209; Officers, 224; President's address (Durant), 161; Secretary's rep., 193; Sections, (officers), 226, (programs and abstracts), 211; Treasurer's rep., 195
Connective tissue, heritable disorders, 112
Cooper, D. A., 223, 225*
Cowan, A., 94, 179
Cowan, T. H., 226*
Cracovaner, A. J., 212
Crane, A. R., 210, 224*

Davidson, W. D., 88
Davis, A. C., 212
Davis, R. A., 212
Deaver, J. M., 225*, 226*
Declomycin, ocular penetration, 212
Dehne, T. L., 225*
Diabetes mellitus, serum lipids, 217
Dietrich, H. J., Jr., 226*
Di George, A. M., 90, 215
Dreifus, L. S., 83, 217
Dressing carriage, Morton, 153
Duarte, C., 83
Durant, T. M., 81, 160, 224*

Ear, aneurysm, 213, middle ear disease, 213, otosclerosis, 213, tests, 213
Elkins, C. M., 217
Elliott, F. A., 212
Elsom, K. A., 224*
Erslev, A. J., 214
Erythropoiesis, ineffective, 81
Eye, cataract, 212, evisceration, 212, glaucoma, 212, iris, 212, macula, 212, malignant exophthalmos, 212, papilledema, 212, retinal detachment, 212,

photocoagulation, 212, tonometry, 212, trauma, 212

Fabritius, R. E., 212
Farrar, G. E., Jr., 224*
Fellows, list of, 227
Fetter, T. R., 99
Finley, J. K., 212
Fischer, C. C., 224*
Fisher, G. R., III, 81
Frankl, W. S., 86
Frayer, W. C., 212
Furgiuele, F. P., 212

Ghana, health problems, 17
Gibbon, J. H., Jr., 224*
Gill, R. J., 226*
Gilroy, F. J., 212
Glassman, S., 216
Glover, R. P., memoir of, 191
Glucose determination, simultaneous pleural and venous, 221
Grant, F. C., 211, 225*
Grass, A. D., Rush award, 223
Greenberg, L., 216
Greenberg, S. R., 217
Grove, D. D., 224*
Guanethidine, hemodynamic actions, 88

Hanhausen, E. H., 212
Hanlon, J. J., 81, 226*
Hansen, A. V., 130, 213
Harkins, H. P., 213
Harrell, J. D., 71
Hatfield lecture, Witt, P. N., 9
Haurani, F. I., 81
Health, sciences (Burney), 164; American (Rutstein), 170; periodic examinations, 213
Hedges, T. R., Jr., 212
Heredity, connective tissue disorders, 112
Hewson, W., memoir of, 156
Histidinemia, 215
Hitchens lectures, Sodeman, W. A., 17; Burney, L. E., 164
Hodes, P. J., 225*
Hollander, J. L., 225*
Howard, J. M., 225*, 226*
Howell, J. C., memoir of, 185
Huber, J. F., 208, 224*
Hyman, H. L., 225*
Hypertension, guanethidine therapy, 88
Hypoglycemia, leucine-induced, 90

Imbriglia, J. E., 224*
Infection, mouse polyoma virus, 66, salmonella, 86, herpetic, 212
Influenza, 1918 pandemic, 212
International health, 17, 164
Iossifides, I. A., 214
Israel, H. L., 211

Jackson, C. L., memoir of, 97; *in memoriam*, 212
Jacobs, M. S., memoir of, 45
Jones, R. K., 213
Joyner, C. R., Jr., 225*

Kaye, R., 81
Kern, R. A., 224*, 226*
Kety, S. S., Alvarenga prize lecture, 101
Kidney, function tests, 83
Kirshner, R. J., 212
Kitchell, J. R., 191
Klauder, J. V., 81
Klenk, E. L., 213
Kline, O. R., 226*
Kline, S. R., 217
Klotz, R. G., Jr., 217
Krumbhaar, E. B., prize essay IV (Harrell), 71, 224*

Lang, O. E., 226*
Laws, G. M., 184
Leopold, I. H., 212
Lewis, J. P., memoir of, 184
Library: ann. rep., 200; committee, 224*
Likoff, W. L., 211, 217
Lindsay, J. R., 213
Liver, circulation, 49, function, 49
Lubowitz, R. M., 212
Ludwig, G. D., 219

Mabry, C. C., 90
Machella, T. E., 194, 224*
MacNeal, P. S., 226*
Macroglobulinemia, 88
Marden, P. A., 226*
Mathews, R. A., memoir of, 187
Mays, R. W., 225*
McCarrison, R., memoir of, 39
McCouch, E. A., 226*
McCreary, T. W., 223
McDaniel, W. B., 2d, 205, 226*
McElfresh, A. E., 211
McGarry, T. S., 217
McKusick, V. A., Anders lecture, 112
Mead, Kate Hurd, lecture, Wright, A. D., 22
Medical Documentation Service, 205
Mellville, P. J., 213
Meltzer, P. E., 213
Memoirs
Bower, J. O., 48
DeLong, P., 179
Glover, R. P., 191
Hewson, W., 156

Howell, J. C., 185
Jackson, C. L., 97
Jacobs, M. S., 45
Lewis, J. P., 184
Matthews, R. A., 187
McCarrison, R., 39
Mullen, C. R., 99
Newcomet, W. S., 41
Norris, C. C., 158
Paschkis, K. E., 95
Stokes, J. H., 180
Williams, C. S., 94
Mental illness, biochemistry, 101; chronic, 127; hospital care, 127; music therapy, 130
Merrill, J. P., Alvarenga prize lecture, 1
Miller, M. M., 224*
Miller, T. G., 224*, 225*
Montgomery, H., 224*
Morse, D. P., 211
Morse, E. H., 208, 226*
Morton, T. G., blood transfusion, 137, dressing carriage, 153
Moskowitz, R. W., 213
Moyer, J. H., 83, 88
Mütter lecture, Blumberg, J. M., 223
Mütter Museum: annual report, 209; committee, 224*
Muirhead, J. F., 212
Mullen, C. R., memoir of, 99
Music, therapy in mental hospital, 130
Myerson, R. M., 211

Newbold lectures, Brauer, R. W., 49; Rowe, W. P., 66
Newcomet, W. S., memoir of, 41
Newton, D., 212
New York Academy of Medicine, Section on Otolaryngology, 213
Nichols, H. T., 218
Nickel, sensitivity, 81
Nodine, J. H., 211
Norris, C. C., memoir of, 158
Norris, C. M., 97
Norris, R. F., 224*
Novack, P., 88

Olsen, A. K., 225*
Ophthalmological cases, 212, 213
Opium, history of, 22
Ornsteen, A. M., 225*
Osler, W., student's note book, 77

Padis, N., 213, 226*
Pancreas, tolbutamide test, 216
Parathyroid gland, function in metastases, 219
Parkhurst, L. W., 213
Parkinson, W. N., Strittmatter award, 223
Paschkis, K. E., memoir of, 95
Pastor, B. H., 218
Pennsylvania Public Health Association, Reg. 1, 164
Periarteritis nodosa, review of 56 cases, 213
Periodic disease, 215
Perkins prize, (III) Klenk, E. L., 213
Peterson, L. H., 225*
Philadelphia County Medical Society, Eye Section, 212; Laryngological Society, 213; Joint Meetings, 213; Rush awards, 223; Strittmatter award, 223
Philadelphia Laryngological Soc., 213
Philoctetes, sickness of, 71
Physick, P. S., friendship with B. Rush, 28
Pillsbury, D. M., 180
Practice, medical standards, 170
President's address, (Durant), 160
Psychiatry, contributions of biochemistry, 101

Radbill, S. X, 45, 77, 224*
Ravdin, R. G., 213
Rawnsley, H. M., 81, 211
Reimann, H. A., 215
Resnick, M. E., 218
Rhoads, J. E., 224*, 225*
Richman, M. W., 212
Roberts, B., 225*
Robertson, H. F., 48
Rodman, T., 218
Roediger, P. M., 217
Rogers, F. B., 39, 86, 224*, 225*, 226*
Rollin, H. R., 130
Rommel, E., biography, 212
Rosenfeld, J., 83
Rowe, W. P., Newbold lecture, 66
Royster, H. A., 225*
Rupp, J., 225*
Rush, B., awards, 223
Rush, B., friendship with P. S. Physick, 28
Russia, laboratory medicine, 223
Rutstein, D. D., 170

Sachs, M. L., 91
Sallman, L. V., 212
Salmonellosis, contaminated fish, 86
Sarin, L. K., 212
Schaeffer, J. P., 224, 226*
Scheffey, L. C., 158, 224*, 225*
Scheie, H. G., 212, 226*
Schepens, C. L., 212
Schnabel, T. G., 185, 224*, 225*
Schnabel, T. G., Jr., 226*
Schneeberg, N. G., 81
Schreader, C. J., 226*
Schreck, K. M., 225*
de Schweinitz lecture, 212
Schweitzer, A. L. P., honorary foreign fellow, 250
Seaman, D., 212
Secretary's report, 193
Sections of the College; officers, 226*; programs and abstracts, 81, 211
Sery, T. W., 212

Sharpe, W. D., 137
Sheldon, G. F., 28
Shuman, C. R., 226*
Silcox, L. E., 213
Smith, A. T., 156
Smith, B. D., Rush award, 223
Sodeman, W. A., Hitchens lecture, 17, 225*
Soloff, L. A., 81
Spaeth, E. B., 226*
Starr, I., 225*
Stauffer, H. M., 84
Steiger, W. A., 225*, 226*
Stokes, J. H., memoir of, 180
Strittmatter award, W. N. Parkinson, 223
Sturgis, S. B., 226*
Sullivan, R. D., 213
Sunderman, F. W., 81
Sunderman, F. W., Jr., 81
Syndrome, Loeffler's, 81; primary hypoaldosteronism, 82; macroglobulinemia, 88, ruptured chordae tendinae, 218

Tassman, I. S., 226*
Templeton, J. Y., III, 225*
Thompson, C. M., 226 (present. Strittmatter)
Thrombosis, right auricular, 89
Thyroid gland, function, 220, thyrotropin, 220, thyroxine, 220
Thyrotropin, thyroid function, 220
Thyroxine, analogues in cardiovascular diseases, 91
Tittle, C. R., Jr., 211
Tocantins, L. M., 81
Toole, J. F., 226*
Tourtellotte, C. D., 215
Tranquilizers, experimental proof of specificity, 9
Transfusion, blood, 137
Transplantation of tissues, 1
Treasurer's report, 195
Tristan, T. A., 81
Tumors, mouse polyoma, 66, nasopharynx, 213, cancerocidal drugs, 213

Urbach, F., 211
Urbach, J., 211
Urrichio, J. F., 218

Vastine, J. H., 2nd, 199
Virus, mouse polyoma, 66, herpes, 212

Wade, E. N., 210, 226*
Waldman, M., 217
Watanabe, Y., 217
Whayne, T. F., 225*, 226*
Williams, C. S., memoir of, 94
Williams, J. C., 224*
Winchester, R. A., 213
Wise, R. I., 225*
Witt, P. N., Hatfield lecture, 9
Wolferth, C. E., Jr., 225*
Wolkowicz, M. I., 212
Woloshin, H. J., 86
Wood, F. C., 211, 225*
Wright, A. D., Mead lecture, 22

Young, J. R., physiologist, 211

Zatuchni, J., 90, 225*

Vol. 29, No. 1
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July
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TRANSACTIONS & STUDIES

of the

College of Physicians of Philadelphia

Contents

Transplantation of Tissues (*Alvarenga Prize Lecture XX*)
John P. Merrill 1
Tranquilizers: Experimental Proof of their Specific Effects (*Nathan Lewis Hatfield Lecture XLV*) . . . . . Peter N. Witt 9
Africa Today—Health and Environmental Influences (*Arthur Parker Hitchens Lecture V*) . . . . . William A. Sodeman 17
The History of Opium (*Kate Hurd Mead Lecture XIII*)
Arthur Dickson Wright 22
Rush and Physick: An Important Medical Friendship
George F. Sheldon 28

Memoirs:
Sir Robert McCarrison (1878–1960) . . . . . Fred B. Rogers 39
William Stell Newcomet (1872–1960) . . . . Eugene P. Pendergrass 41
Maurice S. Jacobs (1897–1960) . . . . . Samuel X Radbill 45
John Oscar Bower (1885–1960) . . . . . Harold F. Robertson 48

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Vol. 28, No. 4, April, 1961

Contents

Annual Report of the President ..... Jonathan E. Rhoads 149
Inaugural Remarks ..... Thomas M. Durant 154
Two Landmarks in American Medicine—Their Impact
Truman G. Schnabel 156

Memoirs

Charles Howard Miner (1868–1959) .... George Morris Piersol 164
Louise Pearce (1885–1959) ..... Marion S. Fay 167
William Daniel Stroud (1891–1959) ..... Charles C. Wolferth 169
Myer Solis-Cohen (1877–1960) ..... Jesse T. Nicholson 171
David Nathaniel Kremer (1890–1960) ..... Truman G. Schnabel 173
George N. J. Sommer, Sr. (1874–1960) ..... I. S. Ravdin 174

Annual Reports

Treasurer, 175; Library, 179; Mütter Museum and College Collections, 188.

Census of Incunabula in the College Library, Supplement I, 1960 191
Transactions of the Sections: Programs, and Abstracts from the Section on General Medicine 193
List of College Lectures, 1960 223
Officers, Committees, Sections, and Administrative Staff of the College, 1961 224
List of Fellows 228
Suggested Form of Bequest 252
Index to Volume 28 253

Vol. 29, No. 4 (4th Series) INDEX NUMBER April 1962

TRANSACTIONS & STUDIES

of the

College of Physicians of Philadelphia

Contents

Annual Report of the President . . . . . Thomas M. Durant 161
The Health Sciences—A Common Bond Among All Nations (*Arthur Parker Hitchens Lecture VI*) . . . . . Leroy E. Burney 164
Better Health for Americans: The Need for Standards of Medical Care (*James M. Anders Lecture XLI*) . . . . . David D. Rutstein 169
Memoirs
Perce De Long (1880–1961) . . . . . Alfred Cowan 179
John Hinchman Stokes (1885–1961) . . . . . Donald M. Pillsbury 180
James Poland Lewis (1901–1961) . . . . . George M. Laws 184
John Carnett Howell (1901–1961) . . . . . Truman G. Schnabel 185
Robert A. Matthews (1903–1961) . . . . . Kenneth E. Appel 187
Robert P. Glover (1913–1961) . . . . . J. Roderick Kitchell 191
Annual Reports
Secretary, 193; Treasurer, 195; Library, 200; Mütter Museum and College Collections, 209.
Transactions of the Sections: Programs, and Abstracts from the Section on General Medicine 211
List of College Lectures, 1961 223
Officers, Committees, Sections, and Administrative Staff of the College, 1962 224
List of Fellows 227
Suggested Form of Bequest 251
Index to Volume 29 252

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Preceding Number

Vol. 29, No. 3, January, 1962

Contents

Contributions of Biochemistry to Psychiatry (*Alvarenga Prize Lecture XXI*) . . . . . Seymour S. Kety 101

Heritable Disorders of Connective Tissue (*James M. Anders Lecture XL*) . . . . . Victor A. McKusick 112

Management of the Chronic Mentally-Ill . . . . . William P. Camp 127

Therapeutic Use of Music in a Mental Hospital . . . Henry R. Rollin 130

Thomas G. Morton and Blood Transfusion: 1869–1878. William D. Sharpe 137

A Note on the Morton Dressing Carriage . . . . . John B. Blake 153

Memoirs:

William Hewson (1884–1960) . . . . . Austin T. Smith 156

Charles Camblos Norris (1876–1961) . . . . . Carl Bachman 158

c. 64

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